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Special issue: Neurobiology of temperament, personality and psychopathology: what's next?

Title: Gut microbiome-brain axis and inflammation in temperament, personality and psychopathology

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Abstract

Full understanding of temperament, personality and psychopathology must consider biological mechanisms beyond the brain. Over 4000 species of commensurate microbiota inhabit our bodies and influence almost all aspects of human physiological function. Evidence supports bidirectional relationships between the gut microbiome and brain function. For example, gut environment directly influences limbic function via the vagal nerve, modulating affect and stress-responsivity. In turn, states of distress affect the ecology of the gut, physiologically and through behavioural alteration (diet, social interaction). Furthermore, the gut microbiome modulates the release of inflammatory molecules and hormones, indirectly affecting brain structure and function. Thus, development of gut microbiome from gestation, through birth, during childhood, adulthood and into old age is associated with temperament, personality and psychological wellbeing, including sexual differentiation in psychological function during puberty, and vulnerability to developmental, psychiatric and neurological disorders. Moreover, nutrients known to affect gut function and inflammation (e.g., fatty acids) are associated with temperament and personality in clinical and nonclinical groups. These relationships may reflect the influence of psychological traits on the microbiome by determining how an organism explores the environment, seeks reward, its social interaction and food preferences. However, it might also reflect an effect of microbiome status on psychological function. There is a need for further systematic multidisciplinary studies that integrate psychology, neurosciences, immunology and microbiology to determine the direction of these relationships and fully understand the biological basis of temperament, personality and psychopathology.

Disciplines covered: neuroanatomy, psychiatry, endocrinology, psychology, personality, immunology, gastroenterology; neuroimaging, neurotransmitter function

Introduction

Substantial advances in understanding brain networks underpinning temperament, personality[1] and psychopathology have been made over the last few decades [1,2]. However, recent evidence suggests that a full understanding of what makes us 'us', may require consideration of biological mechanisms beyond the brain [3,4]. Over 4000 commensurate microbiota species inhabit our bodies, influencing almost all aspects of human physiological function. Indeed, only 1% of the combined human and microbial DNA in our bodies is human. Given temperament and personality affect perceived threat (Neuroticism), social (Extraversion) and environmental (Openness) interaction, the resulting physiological and behavioural changes may influence the gut microbiome (i.e., the gut microbial community, including genetic components, microbial biodiversity, and their resulting functionality) [5]. This, in part, contributes to the remarkable individual differences in gut microbiome diversity and composition, which influences physical and psychological health [3,6]. In turn, the gut microbiota might also influence temperament and personality, via bidirectional communication with the brain [3,7], involving both direct (cranial nerve X) and indirect (e.g., via immune and endocrine systems) pathways [8]. Thus, the gut may represent a missing link between psychological traits and health. The current manuscript reviews evidence in this field that is rapidly gaining ground in neuroscience, psychology and mental health [9].

Gut microbiome development

The gut contains 10^{13} microorganisms with over 1000 unique bacterial species, comprising four major phyla: Firmicutes (e.g., *Lactobacillus*, *Lachnospira*, *Veillonella*, *Eubacterium*, *Roseburia*, *Ruminococcus*), Bacteroidetes (e.g., *Bacteroides*, *Parabacteroides*), Actinobacteria (e.g., *Bifidobacterium*) and Proteobacteria (several gram-negative pathogens e.g., *Escherichia-Shigella*, Gammaproteobacteria). Infants receive the majority of their initial microbiome via the mother during, and possibly prior to, birth [10]. Several factors - mode of birth (vaginal, C-section), duration of gestation, antibiotic exposure, nutrition, genetics, social and environmental interaction, trauma/stressor exposure (to name a few; [11,12]) - influence an intense period of infant microbiome development, that is intertwined with early brain [13] and immune system development [14,15]. The gut microbiome stabilises by 3 years to resemble the young adult composition [8,10], at which time it is predominantly determined by horizontal transmission (e.g., social contact [7]), but follows various age-related milestones throughout life [16].

Early infant microbiome is characterised by an abundance of *Bifidobacterium* (due to a predominantly milk-based diet). As the child explores other foods (e.g., starches) and environments, *Bacteroides* (and other genera) increase, and the microbiome becomes more diverse. Whilst transition to a *Bacteroides*-dominated community at 12 months has been associated with better cognitive development at 24 months [17], other genera and specific

[1] Whilst overlap between the terms temperament and personality is acknowledged, the authors view temperament as emerging earlier in ontogenetic development and continuing throughout life, whilst more complex personality traits emerge with the development of executive function and the social brain. Thus, currently, we refer to temperament in sections on infancy and childhood, whilst in sections on adulthood we refer to personality.

species remain important determinants of health (e.g., *Bifidobacterium*, *Lactobacillus*) and illness (e.g., several Proteobacteria). In adults, distinct entero-types (e.g., characterised by a predominance of *Bacteroides*, *Prevotella* or *Ruminococcus*) have been proposed that depend in part on the hosts' long-term diet (and thus, culture [16,18] and personality, e.g., openness) and show different patterns with regard to emotion processing, brain function and vulnerability to psychopathology [19].

Microbiome and early life temperament

Regarding infant (18–27 months) temperament [20], microbiome phylogenetic diversity is associated with Surgency/Extraversion [21]. In boys only, Surgency/Extraversion has been associated with overall diversity and relative abundances of certain Firmicutes (*Dialister*, Ruminococcaceae) and Bacteroidetes (Rikenellaceae, *Parabacteroides*). This latter finding was in part associated with age and diet, while the relationship between phylogenetic diversity and Surgency (Extraversion) seemed unaffected by these variables. Although the directionality of these associations is unclear, they may reflect a tendency towards high levels of positive affect, engagement with the environment, and activity [21]. In another study an abundance of *Bifidobacterium* (and *Streptococcus*) assessed at 2.5 months was associated with later Surgency assessed at 6 months [22], whilst higher *Bifidobacterium* and Enterobacteriaceae (and lower *Bacteroides*) was associated with Regulation.

Gut-microbiome-brain research is vulnerable to inter-study inconsistency on many levels, not in the least due to methodological differences in measurement of microbiota and psychological function [23]. Indeed, distinct species in the same genus differentially associate with psychological function. For example, impulsivity in childhood is positively associated with *Bacteriodes xylanisolvens,* but inversely with *Bacteriodes fragiles* [24]. Thus, associations based on phyla and genera, might be less consistent than those that group microbiota based on functional properties, for example, production of short chain fatty acids (e.g., butyrate), bile and/or pro/anti-inflammatory molecules, which influence physiology and behaviour [25].

Individual differences in study populations (sex, diet, age, enterotype) might also lead to apparently inconsistent findings. For example, girls (18–27 months) show a different pattern to boys with inverse associations between phylogenetic diversity (Shannon Diversity Index) and effortful control, and positive associations between Beta diversity and fear reactivity [21]. This is in line with animal studies showing that associations between the gut and behaviour are sex dependent [26,27], and suggest that in humans, such differentiation begins prior to puberty.

As diet diversifies and the infant brain develops, the role of the gut in regulating negative emotions may vary. Thus, in new-borns (25 days old), *Bifidobacterium* enrichment is associated with negative emotionality (*Bifidobacterium pseudocatenulatum*) and emotion regulation/orienting (*Bifidobacterium pseudocatenulatum* and *Bifidobacterium catenulatum*). However, in infants, an abundance of *Bifidobacterium* (along with lower *Clostridium*) at 2.5 months has been associated with reduced "fear bias" (i.e., attention toward fearful versus happy/neutral faces) at 8 months [28]. Similarly, in a Chinese cohort (12 months olds), *Bifidobacterium* was related with Soothability [29], whereas Hungatella (also

associated with constipation and eczema in children [30]) was associated with reduced Cuddliness. Indeed, several other families and species have been associated with the fear response, such as Rikenellaceae (18–27 months old girls [21]), *Parabacteroides distasonis*, *Bilophila unclassified, and Roseburia intestinalis* (5-7 year olds [24]), and Lachnospiraceae and *Bacteroides* (in 5-11 year olds were associated with activation of frontal networks in response to fear [11]). Whilst these studies highlight the possibility that gut microbiome composition from infancy directs development of temperament, clearly further hypothesis-driven work using standardised protocols is needed in this sparsely investigated field to replicate findings and resolve inconsistencies, control for potential confounding variables (e.g., maternal age, womb environment, diet, virulence etc; [31,32]), and clearly delineate the direction of relationships [23]. Such work is likely to require corroborating human and animal investigations, including dietary intervention and elimination studies, as demonstrated in the case of Autism [33].

Microbiome and personality in adults

Regarding adult personality, Gammaproteobacteria (mostly pathogenic, including *Escherichia coli*) has been associated with Neuroticism (in line with inflammatory models of neuroticism), and indeed major depressive disorder [34,35], whilst Conscientiousness was characterised by lower Proteobacteria, and higher Lachnospiraceae (butyrate-producing bacteria related to anti-inflammatory mechanisms) [36]. Bacterial diversity has been associated with openness and agreeableness, which may reflect a greater tendency for exploration (trying new foods) and social contact. Using home kits for microbiome assays and an online questionnaire in a large cohort (n>600)[2], a composite sociability measure (extraversion, social skills, communication) was associated with a microbiome profile similar to that seen in autism: positive relationship with several genera with anti-inflammatory properties (*Akkermansia*, *Lactococcus,* and *Oscillospira*) and negative association with others implicated in systemic inflammation (*Desulfovibrio*, *Sutterella*). Neurotic tendencies were negatively associated with *Corynebacterium* and *Streptococcus* [7]. In comparison, *Streptococcus salivarius* has been associated with both emotional reactivity and externalising behaviour in children; and *Akkermansia muciniphila* with depression [24]. In older adults, *Megamonas* (Firmicutes with anti-inflammatory action via propionate production) were negatively associated with conscientiousness, neuroticism, and openness, and positively with agreeableness, whilst *Fusobacterium* (opportunistic pathogens) were negatively associated with openness and extraversion [37].

Microbiome, limbic and executive function

The varied relationship between gut microbiota and negative emotionality or fear with age may reflect differential subregion development of limbic networks involved in the response to threat, including those centred around the frontal-medial temporal connections [38] and neuroendocrine systems (i.e., hypothalamus-pituitary-adrenal axis [8]). Whilst development of limbic regions (e.g., amygdala) begins soon after conception, progressive structural and

[2] This study controlled for several potential confounding variables (e.g., sex, age, body mass index, birth delivery mode, type of infant feeding method, antibiotic use etc).

functional segregation between sub-regions' cortical networks continues throughout childhood and adolescence [38,39]). Influence over limbic function by the gut microbiome is supported by several animal studies [8,40] and emerging neuroimaging findings in human infants [41], children [11], and adults [42–44]. For example, Alpha diversity[3] is associated with amygdala-thalamic, anterior cingulate-insula and sensorimotor-inferior parietal connectivity in 1-year olds [41], and might also affect interhemispheric connectivity in newborns [32]. In adults, bacterial microbiota diversity (particularly *Prevotella* and *Bacteroides* abundance) has been associated with insula connectivity with several brain regions [45].

Regarding executive ability, a role has been proposed for *Bacteroides fragilis,* which protects against pathogen induced inflammation, and is positively associated with cognitive control, and inversely with impulsivity and sadness in children [24]. This species also showed weaker inverse associations with aggressive behaviour, emotional reactivity, externalizing behaviour, and incidents of family turmoil. In that study [24], impulsivity was positively associated with *Eubacterium siraeum* and *Bacterioides xylanisolvens,* whilst inhibitory control was inversely associated with *Eubacterium rectale* (a butyrate producer). In response to fear-based stimuli, *Bacteriodes* enrichment was associated with a very specific activation of the medial prefrontal cortex (PFC), whilst Lachnospiraceae enrichment was related to activation in the left lateral PFC, medial PFC, precuneus/cerebellum, and deactivation in the post central gyrus, possibly reflecting frontal control over fear. Concordantly, Lee et al. [19] show that abundance of a novel Lachnospiraceae genus (PAC001043_g taxa) was associated with higher positive affect and lower negative affect. *Lachnospiraceae* is also implicated in interoception, the production of serotonin, adaptive response to stress and pain (along with other family members of the Clostridiales order, e.g., *Ruminococcaceae*) [46], and deficiency may underpin depression [47]. Inflammatory molecules [48], neuropeptides and hormones (i.e., cortisol, ovarian, oxytocin [49]) are regulated by the gut [8] and influence the limbic and executive systems [50,51].

Inflammation

As well as being the principal armament of our physiological defence system, adaptive inflammation collaborates with the microbiome to affect registration of environmental threats and opportunities, biasing perception to promote harm avoidance and facilitate recovery from illness [25]. Indeed, Gassen and Hill [25] suggest a specific adaptive role for inflammation in 'social' perception (punishment and reward) and associated personality traits. For example, the immune system has been implicated as an important determinant of several traits including extraversion, neuroticism, conscientiousness, and emotional response (e.g., anxiety, depression, disgust), motivation, novelty-seeking, self-regulation, and aggression [25,52–54]. Some of these associations may reflect action of inflammatory molecules to inhibit the synthesis of serotonin, leading to a bias towards negative affectivity (e.g., neuroticism). That is, the presence of chronically raised inflammation, as implicated in several non-communicable diseases (physical and psychological), has been shown to alter tryptophan catabolism, reducing serotonergic synthesis and activating kynurenine metabolic pathways. This alters brain chemistry to affect development, increase vulnerability to

[3] Alpha diversity is the ecological diversity of a single sample, taking into account the number of different taxa and their relative abundances.

negative affectivity, damage tissue, and predispose to developmental, psychological and neurological disorders [52,55,56].

On-the-other-hand, dopamine agonism, which is implicated in reward processing and Extraversion, is shown to have anti-inflammatory effects [57]. Thus, brain mechanisms underpinning such traits, may indeed act to protect against chronically raised inflammation, to a certain extent. However, some evidence implies an inverse "U" curve between certain cytokines and personality [25,52–54] as well as cognitive function [58] in the general population, which may be moderated by sex, ethnicity [59], and co-occurring personality traits [60]. Thus, both very low and very high reward sensitivity is associated with elevated inflammation. Important distinctions may be between the 'pleasure' obtained from reward and the 'drive' to obtain reward [61], which are differentiated in more recent developments of reinforcement sensitivity theory (RST; [62]). BAS drive, for example, interacts with ruminative response style to increase inflammatory molecules (e.g., IL-6) in response to social stress [61]. Thus, complex bidirectional relationships exist between the many different inflammatory cytokines, tryptophan catabolites (e.g., Kynurenine, Quinolinic acid) other molecules (e.g., endocannabinoids), distinct subdomains of personality and psychopathology, that some authors have courageously attempted to unravel [52]. Mayer [63] for example, present elegant models of the bidirectional communication between the gut and the brain. Whilst progress has been made with Genome and Connectome projects, we need similar maps of the enteric and immune systems, in relation to temperament, personality and psychopathology, in order to fully understand who we are.

Systemic inflammation is in part determined by the permeability of the gut wall, and thus, microbiome composition, which regulates peripheral intrusion of endotoxins and concomitant immunological responses [64]. However, afferents from the vagal nerve also directly regulate central cytokine synthesis affecting neuroinflammation [25], which may occur in the absence of peripheral response. Thus, whilst supplementation with *Bifidobacterium longum* reduced amygdala hyperactivity in adults with inflammatory bowel syndrome, it did not affect peripheral inflammatory markers [42], suggesting the microbiome may affect limbic function irrespective of systemic inflammation [8].

Furthermore, various psychological routes to illness might operate, that are associated with distinct physiological pathways. For example, Heym et al. [65] show that harsh self-judgement (poor self-compassion), a vulnerability trait for depression, is strongly inversely related to faecal numbers of *Lactobacillus*. This may reflect an observed effect of *Lactobacillus* (along with *Bifidobacterium*) in supporting positive emotional bias [66] and reducing ruminative thoughts [67], but could also be due to the impact of raised psychological stress (e.g., through self-blame) on the ecology of the gut microbiome [68]. Brain networks implicated in self-judgment, self-awareness and self-referential processes (e.g., Insula, ACC, PFC, Amygdala) show strong bidirectional connections with the enteric nervous system (for review see [63]).

Whilst self-Judgement appeared unrelated to a general peripheral marker of inflammation known as C-reactive protein (CRP), CRP (but not *Lactobacillus* or *Bifidobacterium*) was associated with poor cognitive empathy [65], another psychometric vulnerability marker for depression (as well as autism [69], dark personality traits and personality disorders [70,71]). In

Heym et al. [65], cognitive empathy may have acted as a proxy for cognitive flexibility [72], which would hold ties to plasticity (extraversion, openness [73,74]). In line with this, Sumich et al. [75] report associations between plasticity and certain fatty acids with established anti-inflammatory action, whilst those with pro-inflammatory action were associated with Instability (neuroticism, low agreeableness, low conscientiousness). Intake of long chain polyunsaturated omega-3 fatty acids (associated with anti-inflammatory effects) is inversely related to reactive aggression [76] and associated traits [77].

Endocrine Function

Complex relationships exist between the endocrine, enteric and immune systems that influence psychological and physical health [78,79]. Hormones likely act as bidirectional conduits of communication between the microbiome and brain, impacting temperament, personality and vulnerability to psychopathology [79]. For example, sex steroid hormone levels in humans are correlated with gut microbial composition and diversity [80], and animal studies show transference of gut microbiota from male to female rats alters the microbiome and elevates testosterone [81]. Conversely ovarian hormones (e.g., estradiol supplementation) alter gut microbiota, as can stress hormones, such as cortisol, norepinephrine and epinephrine [21]. Thus, following puberty, sex differences in the composition of the gut microbiome become more prominent, reflecting the maturation of microbial, neurological, endocrinological and immunological systems [79,80] and may contribute to subsequent sex differences in psychopathologies [82]. Oxytocin (released during social affiliation) regulates the immune and threat response systems, adaptively improving amygdaloid accuracy in responding to real threats, whilst attenuating response to 'non-threats' [83]. Disentangling causal relationships between these multidirectional systems is in its infancy [23], but urgently required to fully understand mechanisms underpinning temperament, personality and psychopathology.

Pre- and probiotics

With regard to clinical trials in humans, meta-analyses suggest that whilst probiotics [84] have a significant effect on mood in clinical populations [85], their effects in non-clinical populations remain unclear [85]. Nevertheless, some positive findings exist. For example, in Petrochemical workers, probiotic yogurt (*Lactobacillus* and *Bifidobacterium* species) or supplement with several species led to improvement in depression, anxiety and stress [86]. A prebiotic [87] intervention to increase *Lactobacillus* and *Bifidobacterium* species in healthy individuals shifted attention towards more positive stimuli (dot-probe task) and lowered cortisol levels [66]. Marotta et al. [88] recently reported a trial of several *Lactobacillus* and *Bifidobacterium* species in a small group (n=38) of Italian students, in which mood (depression, anger), trait depression, temperament and personality (reinforcement sensitivity) were included as outcomes, along with several other measures (sleep, coping style etc). Clear improvements in profile of mood state (depression, anger and fatigue), but not trait depression, were seen in a group taking probiotics compared to placebo. Moreover, self-reported temperament and personality did not significantly change over the course of the study (9 weeks); unsurprising over such a short period. Such small studies with multiple comparisons are prone to both type I and II errors. On-the-other-hand, whilst studies with

larger sample sizes offer greater power, very large studies are at risk for spurious findings that may reach statistical significance with negligible effect sizes. There is therefore a need for further adequately powered, top-down, hypothesis-driven replication studies.

Summary and Conclusion

Whilst several associations have been identified between the gut microbiome, temperament, personality and psychopathology across the lifespan, the direction of these relationships are currently unknown. At least in part, however, they likely reflect a role for temperament and personality on diversity and composition of the microbiome by influencing social and environmental exploration during development. This may, in turn, influence vulnerability to physical and psychological clinical conditions through alteration in inflammatory environments and regulation of frontal and limbic function. However, further work manipulating the microbiome (through diet or supplementation) over longer periods of time is needed before any conclusions can be drawn about direct effects of the microbiome on temperament and personality.

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References

1. DeYoung, C. G., Grazioplene, R. G., Allen TA: *Handbook of personality: Theory and research*. The Guilford Press; 2021.

2. Cloninger CR, Cloninger KM, Zwir I, Keltikangas-Järvinen L: **The complex genetics and biology of human temperament: a review of traditional concepts in relation to new molecular findings**. *Translational Psychiatry* 2019, **9**:290.

3. Spichak S, Bastiaanssen TFS, Berding K, Vlckova K, Clarke G, Dinan TG, Cryan JF: **Mining microbes for mental health: Determining the role of microbial metabolic pathways in human brain health and disease**. *Neuroscience & Biobehavioral Reviews* 2021, **125**:698–761. (**) This is the most recent comprehensive review that assesses metabolic signatures of different human brain health and disease states.

4. Narengaowa, Kong W, Lan F, Awan UF, Qing H, Ni J: **The Oral-Gut-Brain AXIS: The Influence of Microbes in Alzheimer's Disease**. *Frontiers in Cellular Neuroscience* 2021, **15**.

5. Berg G, Rybakova D, Fischer D, Cernava T, Vergès M-CC, Charles T, Chen X, Cocolin L, Eversole K, Corral GH, et al.: **Microbiome definition re-visited: old concepts and new challenges**. *Microbiome* 2020, **8**:103.

6. Santacroce L, Man A, Charitos IA, Haxhirexha K, Topi S: **Current knowledge about the connection between health status and gut microbiota from birth to elderly. A narrative review**. *Frontiers in Bioscience-Landmark* 2021, **26**:135.

7. Johnson KVA: **Gut microbiome composition and diversity are related to human personality traits**. *Human Microbiome Journal* 2020, **15**:100069.

8. Lerner A, Neidhöfer S, Matthias T: **The Gut Microbiome Feelings of the Brain: A Perspective for Non-Microbiologists**. *Microorganisms* 2017, **5**:66.

9. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K: **Gut Microbes and the Brain: Paradigm Shift in Neuroscience**. *Journal of Neuroscience* 2014, **34**:15490–15496.

10. Walker RW, Clemente JC, Peter I, Loos RJF: **The prenatal gut microbiome: are we colonized with bacteria in utero ?** *Pediatric Obesity* 2017, **12**:3–17.

11. Callaghan BL, Fields A, Gee DG, Gabard-Durnam L, Caldera C, Humphreys KL, Goff B, Flannery J, Telzer EH, Shapiro M, et al.: **Mind and gut: Associations between mood and gastrointestinal distress in children exposed to adversity**. *Development and Psychopathology* 2020, **32**:309–328. (*) Reports on gastrointestinal distress, anxiety, and underpinning brain mechanisms, in children exposed to adversity. Gut microbiota were shown to be associated with prefrontal cortex, precuneus, and posterior cingulate cortex activation to emotional faces presentation.

12. Laursen MF, Bahl MI, Licht TR: **Settlers of our inner surface – factors shaping the gut microbiota from birth to toddlerhood**. *FEMS Microbiology Reviews* 2021, doi:10.1093/femsre/fuab001.

13. Maiuolo J, Gliozzi M, Musolino V, Carresi C, Scarano F, Nucera S, Scicchitano M, Oppedisano F, Bosco F, Ruga S, et al.: **The Contribution of Gut Microbiota–Brain Axis in the Development of Brain Disorders**. *Frontiers in Neuroscience* 2021, doi:10.3389/fnins.2021.616883.

14. Sarkar A, Yoo JY, Valeria Ozorio Dutra S, Morgan KH, Groer M: **The Association between Early-Life Gut Microbiota and Long-Term Health and Diseases**. *Journal of Clinical Medicine* 2021, doi:10.3390/jcm10030459.

15. Więdłocha M, Marcinowicz P, Janoska-Jaździk M, Szulc A: **Gut microbiota, kynurenine pathway and mental disorders – Review**. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2021, **106**:110145.

16. Odamaki T, Kato K, Sugahara H, Hashikura N, Takahashi S, Xiao J, Abe F, Osawa R: **Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study**. *BMC Microbiology* 2016, **16**:90.

17. Carlson AL, Xia K, Azcarate-Peril MA, Goldman BD, Ahn M, Styner MA, Thompson AL, Geng X, Gilmore JH, Knickmeyer RC: **Infant Gut Microbiome Associated With Cognitive Development**. *Biological Psychiatry* 2018, **83**:148–159.

18. Allen AP, Dinan TG, Clarke G, Cryan JF: **A psychology of the human brain-gut-microbiome axis**. *Social and Personality Psychology Compass* 2017, **11**:e12309.

19. Lee S-H, Yoon S-H, Jung Y, Kim N, Min U, Chun J, Choi I: **Emotional well-being and gut microbiome profiles by enterotype**. *Scientific Reports* 2020, **10**:20736.

20. Rothbart MK, Posner MI: **Temperament, Attention, and Developmental Psychopathology**. In *Developmental Psychopathology*. . John Wiley & Sons, Inc.; 2015:465–501.

21. Christian LM, Galley JD, Hade EM, Schoppe-Sullivan S, Kamp Dush C, Bailey MT: **Gut microbiome composition is associated with temperament during early childhood**. *Brain, Behavior, and Immunity* 2015, **45**:118–127. (*) The authors investigated the relation between temperament and gut microbiome in n=77 toddlers, showing that alpha diversity, beta diversity and microbial composition present sex-specific associations with child temperament traits.

22. Aatsinki A-K, Lahti L, Uusitupa H-M, Munukka E, Keskitalo A, Nolvi S, O'Mahony S, Pietilä S, Elo LL, Eerola E, et al.: **Gut microbiota composition is associated with temperament traits in infants**. *Brain, Behavior, and Immunity* 2019, **80**:849–858. (*) Prospective study showing infant microbiome predicts temperament several months later.

23. Hooks KB, Konsman JP, O'Malley MA: **Microbiota-gut-brain research: A critical analysis**. *Behavioral and Brain Sciences* 2019, **42**:e60.

24. Flannery JE, Stagaman K, Burns AR, Hickey RJ, Roos LE, Giuliano RJ, Fisher PA, Sharpton TJ: **Gut Feelings Begin in Childhood: the Gut Metagenome Correlates with Early Environment, Caregiving, and Behavior**. *mBio* 2020, **11**.

25. Gassen J, Hill SE: **Why inflammation and the activities of the immune system matter for social and personality psychology (and not only for those who study health)**. *Social and Personality Psychology Compass* 2019, **13**. (*) Highlights the importance of understanding inflammation and in the range of healthy function as well as psychopathology, with specific regard to social perception, reward and threat responsivity theories.

26. Manosso LM, Lin J, Carlessi AS, Recco KCC, Quevedo J, Gonçalves CL, Réus GZ: **Sex-related patterns of the gut-microbiota-brain axis in the neuropsychiatric conditions**. *Brain Research Bulletin* 2021, **171**:196–208.

27. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan JF: **The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner**. *Molecular Psychiatry* 2013, **18**:666–673.

28. Aatsinki A-K, Kataja E-L, Munukka E, Lahti L, Keskitalo A, Korja R, Nolvi S, Häikiö T, Tarro S, Karlsson H, et al.: **Infant fecal microbiota composition and attention to emotional faces.** *Emotion* 2020, doi:10.1037/emo0000924.

29. Wang Y, Chen X, Yu Y, Liu Y, Zhang Q, Bai J: **Association between Gut Microbiota and Infant's Temperament in the First Year of Life in a Chinese Birth Cohort**. *Microorganisms* 2020, **8**:753.

30. Chan CWH, Leung TF, Choi KC, Tsui SKW, Wong CL, Chow KM, Chan JYW: **Association of early-life gut microbiome and lifestyle factors in the development of eczema in Hong Kong infants**. *Experimental Dermatology* 2021, doi:10.1111/exd.14280.

31. Loughman A, O'Hely M, Vuillermin P: **Letter to the Editor: "Gut microbiota composition is associated with temperament traits in infants."** *Brain, Behavior, and Immunity* 2019, **81**:670.

32. Kelsey CM, Prescott S, McCulloch JA, Trinchieri G, Valladares TL, Dreisbach C, Alhusen J, Grossmann T: **Gut microbiota composition is associated with newborn functional brain connectivity and behavioral temperament**. *Brain, Behavior, and Immunity* 2021, **91**:472–486. (*) This study explored the relationship between microbiome and brain networks in the youngest sample of newborn infants to date, showing that gut microbiota composition is associated with functional connectivity of fronto-parietal and the homologous-interhemispheric networks.

33. Roussin L, Prince N, Perez-Pardo P, Kraneveld AD, Rabot S, Naudon L: **Role of the gut microbiota in the pathophysiology of autism spectrum disorder: Clinical and preclinical evidence**. *Microorganisms* 2020, **8**.

34. Talarowska M, Kowalczyk M, Maes M, Carvalho A, Su K-P, Szemraj J, Gałecki P: **Immune to happiness – inflammatory process indicators and depressive personality traits**. *Archives of Medical Science* 2020, **16**:848–857.

35. Kiecolt-Glaser JK, Derry HM, Fagundes CP: **Inflammation: Depression fans the flames and feasts on the heat**. *American Journal of Psychiatry* 2015, doi:10.1176/appi.ajp.2015.15020152.

36. Kim H-N, Yun Y, Ryu S, Chang Y, Kwon M-J, Cho J, Shin H, Kim H-L: **Correlation between gut microbiota and personality in adults: A cross-sectional study**. *Brain, Behavior, and Immunity* 2018, **69**:374–385. (*) A large (n=672 adults) cross-sectional study of the relationship between microbiome and big-5 personality traits, that attempts to control for several potentially confounding variables.

37. Renson A, Kasselman LJ, Dowd JB, Waldron L, Jones HE, Herd P: **Gut bacterial taxonomic abundances vary with cognition, personality, and mood in the Wisconsin Longitudinal Study**. *Brain, Behavior, & Immunity - Health* 2020, **9**:100155. (*) The authors explored the relation between psycho-cognitive dimensions and gut microbiome in n=313 older adults, reporting association between specific genera and personality, mood and cognitive traits.

38. Gabard-Durnam LJ, O'Muircheartaigh J, Dirks H, Dean DC, Tottenham N, Deoni S: **Human amygdala functional network development: A cross-sectional study from 3 months to 5 years of age**. *Developmental Cognitive Neuroscience* 2018, **34**:63–74.

39. Flannery J, Callaghan B, Sharpton T, Fisher P, Pfeifer J: **Is adolescence the missing developmental link in Microbiome-Gut-Brain axis communication?** *Developmental Psychobiology* 2019, **61**:783–795.

40. Liang S, Wang T, Hu X, Luo J, Li W, Wu X, Duan Y, Jin F: **Administration of Lactobacillus helveticus NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress**. *Neuroscience* 2015, doi:10.1016/j.neuroscience.2015.09.033.

41. Gao W, Salzwedel AP, Carlson AL, Xia K, Azcarate-Peril MA, Styner MA, Thompson AL, Geng X, Goldman BD, Gilmore JH, et al.: **Gut microbiome and brain functional connectivity in infants-a preliminary study focusing on the amygdala**. *Psychopharmacology* 2019, **236**:1641–1651.

42. Pinto-Sanchez MI, Hall GB, Ghajar K, Nardelli A, Bolino C, Lau JT, Martin F-P, Cominetti O, Welsh C, Rieder A, et al.: **Probiotic Bifidobacterium longum NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome**. *Gastroenterology* 2017, **153**:448-459.e8.

43. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain–Raspaud S, Trotin B, Naliboff B, et al.: **Consumption of Fermented Milk Product With Probiotic Modulates Brain Activity**. *Gastroenterology* 2013, **144**:1394-1401.e4.

44. Cowan CSM, Hoban AE, Ventura-Silva AP, Dinan TG, Clarke G, Cryan JF: **Gutsy Moves: The Amygdala as a Critical Node in Microbiota to Brain Signaling**. *BioEssays* 2018, **40**:1700172.

45. Curtis K, Stewart CJ, Robinson M, Molfese DL, Gosnell SN, Kosten TR, Petrosino JF, De La Garza R, Salas R: **Insular resting state functional connectivity is associated with gut microbiota diversity**. *European Journal of Neuroscience* 2019, **50**:2446–2452. (*) The study's findings showed that insular resting state functional connectivity is associated with microbial diversity and structure in healthy adults, reporting differences between non-smokers, tobacco smokers and e-cigarette users.

46. Labus JS, Osadchiy V, Hsiao EY, Tap J, Derrien M, Gupta A, Tillisch K, Le Nevé B, Grinsvall C, Ljungberg M, et al.: **Evidence for an association of gut microbial Clostridia with brain functional connectivity and gastrointestinal sensorimotor function in patients with irritable bowel syndrome, based on tripartite network analysis**. *Microbiome* 2019, **7**:45.

47. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, Wang W, Tang W, Tan Z, Shi J, et al.: **Altered fecal microbiota composition in patients with major depressive disorder**. *Brain, Behavior, and Immunity* 2015, doi:10.1016/j.bbi.2015.03.016.

48. Roth W, Zadeh K, Vekariya R, Ge Y, Mohamadzadeh M: **Tryptophan Metabolism and Gut-Brain Homeostasis**. *International Journal of Molecular Sciences* 2021, **22**:2973. (*) Review framinng the interrelationship between gut function, inflammation and Tryptophan metabolism to idolamines and along Kynureine pathways, with implications for several noncomunicable diseases.

49. Farzi A, Fröhlich EE, Holzer P: **Gut Microbiota and the Neuroendocrine System**. *Neurotherapeutics* 2018, **15**:5–22.

50. Law R, Clow A: **Stress, the cortisol awakening response and cognitive function**. In *International Review of Neurobiology*. . 2020:187–217.

51. Slavich GM, Sacher J: **Stress, sex hormones, inflammation, and major depressive disorder: Extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders**. *Psychopharmacology* 2019, **236**:3063–3079.

52. Heilman P, Hill MN, Coussons-Read M, Brundin L, Coccaro EF: **Role of the kynurenine pathway and the endocannabinoid system as modulators of inflammation and personality traits**. *Psychoneuroendocrinology* 2019, **110**:104434. (*) Delineate interelationship between kynurenine pathways and endocannabinoid systems on temperment and personality in adults.

53. Graham EK, Bastarache ED, Milad E, Turiano NA, Cotter KA, Mroczek DK: **Physical activity mediates the association between personality and biomarkers of inflammation**. *SAGE Open Medicine* 2018, **6**:205031211877499.

54. Wagner E-YN, Ajdacic-Gross V, Strippoli M-PF, Gholam-Rezaee M, Glaus J, Vandeleur C, Castelao E, Vollenweider P, Preisig M, von Känel R: **Associations of Personality Traits With Chronic Low-Grade Inflammation in a Swiss Community Sample**. *Frontiers in Psychiatry* 2019, **10**.

55. Maes M, Kubera M, Leunis J-C: **The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression.** *Neuro endocrinology letters* 2008, **29**:117–24.

56. Fourrier C, Singhal G, Baune BT: **Neuroinflammation and cognition across psychiatric conditions**. *CNS Spectrums* 2019, **24**:4–15.

57. Xia QP, Cheng ZY, He L: **The modulatory role of dopamine receptors in brain neuroinflammation**. *International Immunopharmacology* 2019, **76**.

58. Wang GY, Taylor T, Sumich A, Merien F, Borotkanics R, Wrapson W, Krägeloh C, Siegert RJ: **Associations between immunological function and memory recall in healthy adults**. *Brain and Cognition* 2017, **119**:39–44.

59. Chapman BP, Khan A, Harper M, Stockman D, Fiscella K, Walton J, Duberstein P, Talbot N, Lyness JM, Moynihan J: **Gender, race/ethnicity, personality, and interleukin-6 in urban primary care patients**. *Brain, Behavior, and Immunity* 2009, **23**:636–642.

60. Turiano NA, Mroczek DK, Moynihan J, Chapman BP: **Big 5 personality traits and interleukin-6: Evidence for "healthy Neuroticism" in a US population sample**. *Brain, Behavior, and Immunity* 2013, **28**:83–89.

61. Moriarity DP, Ng T, Curley EE, Anne McArthur B, Ellman LM, Coe CL, Abramson LY, Alloy LB: **Reward Sensitivity, Cognitive Response Style, and Inflammatory Response to an Acute Stressor in Adolescents**. *Journal of Youth and Adolescence* 2020, **49**.

62. Heym N, Lawrence C: **The role of Gray's revised RST in the P-psychopathy continuum: The relationships of Psychoticism with a lack of fear and anxiety, and increased impulsivity**. *Personality and Individual Differences* 2010, **49**.

63. Mayer EA: **Gut feelings: The emerging biology of gut-"brain communication**. *Nature Reviews Neuroscience* 2011, doi:10.1038/nrn3071.

64. Rizzetto L, Fava F, Tuohy KM, Selmi C: **Connecting the immune system, systemic chronic inflammation and the gut microbiome: The role of sex**. *Journal of Autoimmunity* 2018, doi:10.1016/j.jaut.2018.05.008.

65. Heym N, Heasman BC, Hunter K, Blanco SR, Wang GY, Siegert R, Cleare A, Gibson GR, Kumari V, Sumich AL: **The role of microbiota and inflammation in self-judgement and empathy: implications for understanding the brain-gut-microbiome axis in depression**. *Psychopharmacology* 2019, doi:10.1007/s00213-019-05230-2. (**) this is the first study to show a relationship of Lactobacillus spp. with positive self-judgement and reduced affective empathy; and to show that infammation in associated with cognitive empathy in the general population.

66. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PWJ: **Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers**. *Psychopharmacology* 2015, **232**:1793–1801.

67. Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS: **A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood**. *Brain, Behavior, and Immunity* 2015, **48**.

68. Karl PJ, Hatch AM, Arcidiacono SM, Pearce SC, Pantoja-Feliciano IG, Doherty LA, Soares JW: **Effects of psychological, environmental and physical stressors on the gut microbiota**. *Frontiers in Microbiology* 2018, **9**.

69. Andreo-Martínez P, Rubio-Aparicio M, Sánchez-Meca J, Veas A, Martínez-González AE: **A Meta-analysis of Gut Microbiota in Children with Autism**. *Journal of Autism and Developmental Disorders* 2021, doi:10.1007/s10803-021-05002-y.

70. Heym N, Kibowski F, Bloxsom CAJ, Blanchard A, Harper A, Wallace L, Firth J, Sumich A: **The Dark Empath: Characterising dark traits in the presence of empathy**. *Personality and Individual Differences* 2021, **169**:110172.

71. Heym N, Firth J, Kibowski F, Sumich A, Egan V, Bloxsom CAJ: **Empathy at the Heart of Darkness: Empathy Deficits That Bind the Dark Triad and Those That Mediate Indirect Relational Aggression**. *Frontiers in Psychiatry* 2019, **10**.

72. Rodgers J, South M: **Commentary: Thinking flexibly about mental health and autism – a commentary on Ozsivadjian et al. (2020)**. *Journal of Child Psychology and Psychiatry* 2021, **62**:725–727.

73. Mõttus R, Luciano M, Starr JM, Pollard MC, Deary IJ: **Personality Traits and Inflammation in Men and Women in Their Early 70s**. *Psychosomatic Medicine* 2013, **75**:11–19.

74. Jonassaint CR, Boyle SH, Kuhn CM, Siegler IC, Copeland WE, Williams R: **Personality and inflammation: the protective effect of openness to experience.** *Ethnicity & disease* 2010, **20**:11–4.

75. Sumich AL, Matsudaira T, Heasman B, Gow R V., Ibrahimovic A, Ghebremeskel K, Crawford MA, Taylor E: **Fatty acid correlates of temperament in adolescent boys with attention deficit hyperactivity disorder.** *Prostaglandins, leukotrienes, and essential fatty acids* 2013, **88**:431–6.

76. Fido D, Heym N, Bloxsom CAJ, Hunter KA, Gregson M, Sumich A: **Don't slap the fish: The relationship between dietary omega-3 intake and physical aggression is mediated by motor**

inhibition in response to distressed faces. *Personality and Individual Differences* 2021, **169**:110062.

77. Gow R V., Vallee-Tourangeau F, Crawford MA, Taylor E, Ghebremeskel K, Bueno AA, Hibbeln JR, Sumich A, Rubia K: **Omega-3 fatty acids are inversely related to callous and unemotional traits in adolescent boys with attention deficit hyperactivity disorder**. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2013, **88**:411–418.

78. Slavich GM, Sacher J: **Stress, sex hormones, inflammation, and major depressive disorder: Extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders**. *Psychopharmacology* 2019, **236**:3063–3079.

79. Holingue C, Budavari AC, Rodriguez KM, Zisman CR, Windheim G, Fallin MD: **Sex Differences in the Gut-Brain Axis: Implications for Mental Health**. *Current Psychiatry Reports* 2020, **22**:83.

80. Jaggar M, Rea K, Spichak S, Dinan TG, Cryan JF: **You've got male: Sex and the microbiota-gut-brain axis across the lifespan**. *Frontiers in Neuroendocrinology* 2020, **56**:100815. (*) Review that highlights the importance of sex hormones in gut-brain function, and of gut microbiome in regulating sex differences in physiology and behaviour.

81. Wallace CJK, Milev R: **The effects of probiotics on depressive symptoms in humans: a systematic review**. *Annals of General Psychiatry* 2017, **16**:14.

82. Sumich AL, Sarkar S, Hermens DF, Ibrahimovic A, Kelesidi K, Wilson D, Rubia K: **Sex Differences in Brain Maturation as Measured Using Event-Related Potentials**. *Developmental Neuropsychology* 2012, **37**:415–433.

83. Olivera-Pasilio V, Dabrowska J: **Oxytocin Promotes Accurate Fear Discrimination and Adaptive Defensive Behaviors**. *Frontiers in Neuroscience* 2020, **14**.

84. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, et al.: **The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic**. *Nature Reviews Gastroenterology & Hepatology* 2014, **11**:506–514. (*) Provides reccomendations for the definition, development and evaluation of probiotics

85. Goh KK, Liu Y-W, Kuo P-H, Chung Y-CE, Lu M-L, Chen C-H: **Effect of probiotics on depressive symptoms: A meta-analysis of human studies**. *Psychiatry Research* 2019, **282**:112568.

86. Mohammadi AA, Jazayeri S, Khosravi-Darani K, Solati Z, Mohammadpour N, Asemi Z, Adab Z, Djalali M, Tehrani-Doost M, Hosseini M, et al.: **The effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: A randomized, double-blind, placebo-controlled trial in petrochemical workers**. *Nutritional Neuroscience* 2016, doi:10.1179/1476830515Y.0000000023.

87. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, et al.: **Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics**. *Nature Reviews Gastroenterology & Hepatology* 2017, **14**:491–502. (*) Provides reccomnedations for the definition, development and evaluation of prebiotics

88. Marotta A, Sarno E, Del Casale A, Pane M, Mogna L, Amoruso A, Felis GE, Fiorio M: **Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality**. *Frontiers in Psychiatry* 2019, **10**.