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Commentary: Microbial panaceas: does development have the answer? – reflections on Cowan, Dinan, & Cryan (2020)

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Understanding how the microbiome and individual bacterial community members contribute to human health and disease is at the forefront of the microbiota–gut–brain axis field. To date, there has been a good amount of conjecture and empirical work on the causal association of human microbiota with cognition, emotion, and brain function. Some papers have suggested a true paradigm shift in the fields of neuroscience, psychology, and psychiatry, occasioned by data from microbiota–gut–brain interactions (e.g. Mayer et al., 2014). Others have suggested that certain microorganisms might function as 'psychobiotics' – having positive mental health benefits in individuals struggling with mental illness (Dinan, Stanton, & Cryan, 2013). Still others have cautioned against overselling the microbiome and its role in human health, citing a lack of causal studies paired with an excess of review articles, and media-driven hyperbole as potential downfalls within this nascent field (Bik, 2016; Hooks, Konsman, & O'Malley, 2018). What are we to take from these varied perspectives? How can we reconcile the strongly suggestive evidence that the microbiota plays a causal role in mental states (Bercik et al., 2011; Clarke et al., 2013; Hsiao et al., 2013; Neufeld et al., 2011), with the knowledge that the relationship between the microbiota, cognition, emotion, and behavior is likely complex, bidirectional, and heavily mediated by a range of other variables (Hooks, Konsman, & O'Malley, 2018)? In this issue, Cowan and colleagues offer a balanced perspective that acknowledges current limitations in the data (which are expected given the early stage of the field) and propose that considering the role of development can help get us closer to elucidating the full extent of the microbiota's role in health and disease.

Why is a developmental perspective important in microbiota research?

The brain, gut, and thriving mass of bacteria that live inside the gut are intricately connected via a bidirectional communication highway called the microbiota–gut–brain axis. This axis is developmentally constructed in postnatal life, as *in-utero* conditions are considered to be sterile (Escherich, 1989; Goldenberg, Hauth, & Andrews, 2000) or at least extremely low in biomass (Aagaard et al., 2014; Bushman, 2019). While few studies have examined intra-individual microbiota growth across human development (beyond infancy), cross-sectional studies indicate that there is significant maturation in microbiome diversity particularly in the first three years of life (Yatsunenko et al., 2012). Evidence now suggests that the

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microbiota–gut–brain axis continues to mature across middle childhood (Hollister et al., 2015) and into adolescence (Agans et al., 2011; Flannery et al., 2019). In the target review paper, Cowan and colleagues outline the multitude of factors within the developmental environment that are known to influence microbiota, including genetics (Goodrich et al., 2016; Rothschild et al., 2018), diet (Subramanian et al., 2014), mode of birth (Dominguez-Bello et al., 2010; Stewart et al., 2018), and early environmental stress (Callaghan, Fields et al., 2019; D'Agata et al., 2019; Hantsoo et al., 2019). Though limited, together these data support the assertion that the microbiota, its structure and function, is fundamentally a developmental phenomenon. Cowan and colleagues make the strong argument that without understanding how the microbiota constructs itself across human development, and how it responds to expectable and aberrant human environments, we will have little chance of understanding the role it plays in human health and disease in adulthood, or at any stage across the lifespan.

Two important developmental concepts: 'expected environmental input' and 'sensitive periods of microbiota development'

Cowan and colleagues invoke the concept of 'expected environmental input' to explain how there might be a sensitive period of development for the construction of the microbiota–gut–brain axis. This concept is an important one that has been outlined in great detail within the context of visual input and sensitive/critical periods for light-dependent shifts in ocular dominance columns within the visual cortex (Hensch & Quinlan, 2018). By likening the ubiquitous presence of bacteria in the environment to the similarly ubiquitous presence of light, they argue that the microbiota–gut–brain axis might rely on expected colonization events to trigger development, in much the same way as the young visual cortex relies on expected light stimulation to trigger development. An absence of light, or unusual light conditions (i.e. unexpected environmental input), can alter the development of the visual cortex. Cowan and colleagues hypothesize that without bacteria, or with bacterial conditions that are unusual (presumably in the context of our evolutionary history), brain and gut development would also be altered.

There is already much research supporting the hypothesis that the microbiota is an environmental signal that may change development within the wider microbiota–gut–brain axis. Some of the strongest evidence in that domain comes from germ-free animal models. These models demonstrate that an absence of bacteria in early life, but not later in development, alters the maturation of several brain regions with known importance for emotional health, such as the amygdala, hippocampus, ventral striatum, and prefrontal cortex (Vuong et al., 2017). In other words, there appears to be a sensitive period in early life during which bacteria need to be present for brain development to proceed along a typical trajectory. Germ-free rodent models have been criticized for lacking translational potential, because there are very few examples of germ-free conditions in human populations, (Kirk, 2012) and they cannot isolate the mechanism of interest, since the social isolation and immunological changes that germ-free animals experience might also be responsible for alterations in brain development (Al-Asmakh & Zadjali, 2015). Nevertheless, they remain

some of the strongest evidence in support of the microbiota acting as a sensitive period regulator.

The concept of the microbiota acting as an expected environmental stimulus proves very powerful when considering the multitude of emotional and brain health outcomes that have been associated with changes in the microbiota – from Parkinson's disease to anxiety and mood disorders (Hill-Burns et al., 2017; Stevens et al., 2018). Even if we accept that there is indeed a causal relationship between the microbiota and brain, it remains challenging to understand how alterations in the microbiota could be associated with such wide-ranging outcomes. However, by appreciating that the microbiota may act as an expected environmental input, and applying that to the concept of sensitive periods in brain development, a picture emerges in which the type of microbial input at different stages of life might produce very different outcomes depending on what brain regions are most plastic during that time. A related challenge (which could only be overcome with very detailed longitudinal studies – most likely only possible in animal models) is that, because of the programming potential for the microbial environment on brain development, the bacterial conditions that initiated the specific brain trajectory may no longer be evident when the end state (e.g. disorder) in that brain region/circuit/function is reached. As this research field moves forward, the concept of 'expected environmental input' will help build increasingly specific and testable hypotheses about what brain and gut circuits, neurotransmitters, and cell types, will be most affected by the microbiota environment in different stages of early life.

A second important concept brought up by Cowan and colleagues is that the microbiota–gut–brain axis might have its own unique period of heightened sensitivity to environmental input (microbial and otherwise). For example, while the microbiota–gut–brain axis might always be responsive to stress, there may be stages of life when stress causes a particularly pronounced or fundamental change in the function of the axis. These two concepts: (a) that the microbiota is an expected environmental stimulus, influencing the development of the gut–brain axis, and (b) that it has its own period/s of heightened plasticity, making it malleable to different environments, together highlight the dynamic and bidirectional nature of the microbiota across development. Moreover, they illustrate the nuanced but critical point that disentangling cause and effect is incredibly difficult in this system, but is made even more so when the dynamic developmental nature of these processes is not considered.

Words of advice for developmental research on the microbiota–gut–brain axis

While Cowan and colleagues do promote developmental research on the microbiota–gut–brain axis, they are also careful to highlight many of the potential pitfalls of microbiota research within development and provide helpful advice for avoiding them. Two of their most important recommendations involve (a) the use of cross-species translational models in development, and (b) a movement toward more justified research decisions. In terms of the former, the authors acknowledge the importance of cross-species (typically rodent and human) work in this field and also discuss how challenges inherent to cross-species

translational research are amplified when one must consider the development of the microbiota, gut, and brain together. Several methods for aligning age in cross-species translational work have been developed for brain and behavior, which rely on ecological approaches (Callaghan, Meyer et al., 2019), or macro/micro anatomical changes in the brain (Clancy et al., 2007). Should we now also think about aligning species based on the stage of gastrointestinal or microbiota development? Is it even possible to do so? Rather than providing solutions to this very complicated problem, Cowan and colleagues instead call for greater consideration of the multitude of non-brain systems that might be divergent across species in development, and which could influence the outcomes and interpretation of such translational studies.

In terms of their second piece of advice, Cowan and colleagues describe certain practices researchers should follow, including justifying the probiotic strains used in research, the specific bacteria targeted in analyses, and the kingdoms targeted in microbiome analyses (e.g. bacteria, as opposed to fungi and viruses), and describing whether analyses are hypothesis-driven or exploratory. Indeed, researchers for this emerging field of microbiota–gut–brain science have recently advocated for institution of ‘open science’ practices (Aarts & El Aidy, 2019; Caporaso et al., 2010; Johnstone & Kadosh, 2019), such as study and analysis preregistration, as well as open access to data and analysis pipelines (Aarts & El Aidy, 2019; Caporaso et al., 2010; Johnstone & Kadosh, 2019). For researchers starting out in the field, standard adherence to these practices can help build a community where robust effects can be discovered and their further investigation accelerated.

As a final word of advice, not explicitly stated in the Cowan review, it is worth noting that even when not the focus of investigations, the microbiota might be (at best) a hidden source of variability in study outcomes, or even act to obscure relationships between outcome and predictor variables. As such, even for researchers who are not interested in studying the microbiota *per se*, our expanding knowledge on its importance in health, disease, and development is a reason enough to stay abreast of new discoveries in the field.

Clinical implications of microbiota–gut–brain axis research?

There is no doubt that the microbiota–gut–brain axis has captured the collective attention of psychology, psychiatry, neuroscience, as well as the general public. The idea that we might be able to affect our brain and behavior by manipulating the microbiota is exciting and holds enormous clinical potential. Reading some of the popular press, one might get the sense that microbiota manipulations have the potential to become a virtual panacea, being associated with disorders as diverse as multiple sclerosis, anxiety and mood, attention deficits, and schizophrenia (Costandi, 2017). However, as succinctly stated by Cowan and colleagues, ‘the state of the research has not yet reached the stage where recommendations can be made for the use of microbiota-based medicines or diagnostics in clinical settings’. Not only are we still trying to move past correlations and understand the complex web of causality, but there are fundamental aspects of the microbiota–gut–brain axis that we do not yet understand. For example, while manipulating the microbiota with probiotics is generally seen to have only positive (or in the worst case, negligible) outcomes for human health, some animal models have shown that probiotic treatment can produce unexpected (and

possibly undesirable outcomes) on memory (Beilharz et al., 2018). Considering these data and the early stage of current research in the microbiota–gut–brain axis, caution is warranted in translating potential therapeutics from emerging findings. By adopting a neurodevelopmental approach, and writing this primer for the field of developmental psychopathology, Cowan and colleagues provide the background and tools needed to accelerate the accumulation of actionable knowledge on microbiota–gut–brain axis development.

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