



## Conference on ‘Diet, nutrition and mental health and wellbeing’ Optional symposium

### Food and the gut: relevance to some of the autisms

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Complex, diverse and rarely appearing without comorbidity, the autism spectrum disorders continue to be a source of research interest. With core symptoms variably impacting on social communication skills, the traditional focus of many research efforts has centred on the brain and how genetic and environmental processes impact on brain structure, function and/or connectivity to account for various behavioural presentations. Alongside emerging ideas on autistic traits being present in various clinical states, the autisms, and the over-representation of several comorbid conditions impacting on quality of life, other research avenues have opened up. The central role of the brain in relation to autism may be at least partially influenced by the functions of other organs. The gastrointestinal (GI) tract represents an important biological system pertinent to at least some autism. The notion of a gut–brain–behaviour axis has garnered support from various findings: an overrepresentation of functional and pathological bowel states, bowel and behavioural findings showing bidirectional associations, a possible relationship between diet, GI function and autism and recently, greater focus on aspects of the GI tract such as the collected gut microbiota in relation to autism. Gaps remain in our knowledge of the functions of the GI tract linked to autism, specifically regarding mechanisms of action onward to behavioural presentation. Set however within the context of diversity in the presentation of autism, science appears to be moving towards defining important GI-related autism phenotypes with the possibility of promising dietary and other related intervention options onward to improving quality of life.

**Autism: The autisms: Brain: Comorbidity: Gastrointestinal tract: Bowel: Diet: Gluten: Casein: Milk**

It would not be out of place to suggest that the cumulative results of the huge research efforts dedicated to the autism spectrum disorders down the years have probably created less certainty about what we know about the condition(s). Autism continues to be diagnosed solely on the basis of observable behaviours and recorded/remembered developmental history similar to when first formally described over 80 years ago<sup>(1)</sup>. Identifying core symptoms in the areas of social and communicative functions remains one of the few facts known about autism<sup>(2)</sup> as proposed genetic and biological tests have come and gone. In light of the increasingly popular notion of plurality<sup>(3)</sup> where autistic traits are seemingly present in various different conditions, the autisms, it is perhaps

becoming less and less likely that a universal biological test for autism will ever be successfully developed despite multiple lay media headlines intimating how close science is to achieving such a goal based on measures of brain function or eye tracking for example.

What is becoming clear is that autism or autism spectrum disorders as a diagnostic label serves a purpose in identifying those people presenting with the cluster of symptoms included under it but seemingly has little function (validity) as a starting point when it comes to determining underlying genetics or biology<sup>(4)</sup>. The heterogeneity present throughout the autism spectrum is further complicated by a myriad of overrepresented comorbid labels accompanying a diagnosis<sup>(5)</sup>. Said

**Abbreviation:** GI, gastrointestinal.

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comorbidity variably impact on quality of life, sometimes more significantly than the autism diagnosis itself. Coupled also to extensive evidence on differing developmental trajectories being present in autism<sup>(6)</sup> and the problems facing autism research are multiple and complex when specifically reliant on the use of the singular-label 'autism' as a research starting point.

### The brain and autism

The structure and function of the brain in relation to autism has enjoyed a privileged research position down the years. It is natural to assume that the brain plays an important role in the presentation of autism given its behavioural focus. Such research has spurred a revolution in our thinking about autism, as the concept of 'neurodiversity' has risen in prominence highlighting heterogeneity. It has also witnessed the increasing use of more problematic terms such as 'neurotypical' to somehow differentiate brain or thinking styles in autism from not-autism in a binary fashion. Such terminology runs counter to the understanding that 'typical' is not something that can yet be suitably defined in relation to the brain in any population; also taking no account of fluidity in behaviour and brain function as a consequence of maturation or the presence of comorbid conditions or other allied factors.

Alongside the rise and rise of technological advances providing insights into the inner workings of the brain, significant resources continue to be ploughed into examination of this important organ with autism in mind<sup>(7)</sup>. Challenges remain however in interpreting data derived from such imaging studies of the brain with a focus on autism, also not helped by sweeping generalised theories of brain structure or function in relation to autism<sup>(8)</sup>. The idea of an 'autistic brain'<sup>(9)</sup> to denote generalised differences in structure or function to account for autistic behaviours again offers only a simplistic explanation for an issue of significant complexity. This and many other areas of autism science it seems, continue to ignore the quite remarkable heterogeneity present alongside the label, including also the fact that conditions such as epilepsy/seizure-disorder also known to affect brain functioning are among one of the most important comorbidities accompanying autism<sup>(10)</sup>.

### The gastrointestinal tract and autism

Of the many scientific advances that are being made in relation to autism (i.e. that the presence of comorbidity is the rule rather than the exception), there is an increasing realisation that the brain may not be the only organ relevant to (some) autism. The gastrointestinal (GI) tract has been discussed with reference to autism for many years. Some of the most prominent people central to the history of autism spectrum disorders have talked about how facets of GI functioning may not be totally unrelated to at least some cases of autism<sup>(11)</sup>. In more recent times, discussions have focused on several aspects

of GI functioning as being potentially relevant to (some) autism based on various strands of peer-reviewed evidence<sup>(12)</sup>. This includes: the overrepresentation of functional and pathological bowel states in cases of autism<sup>(13,14)</sup>, the impact of various dietary interventions for autism<sup>(15)</sup> and the new triad comprising GI immune function–intestinal barrier permeability–gut microbiota<sup>(16)</sup> potentially being relevant to some of the autisms.

### The gut–brain–behaviour axis and (some) autism

The idea of a gut–brain–behaviour axis in relation to autism derives evidence from various different sources. The GI tract is at its most basic an energy-converting device. Using food and drink as fuel, this complicated organ performs countless duties to release energy from diet to drive/maintain the various biological systems of the body including the brain. Food therefore represents an important variable in any discussions about the GI tract.

It has long been known that certain foods when meeting certain GI tracts can cause issues in relation to physical health as per the example of the diet-related autoimmune condition coeliac disease. No less important is the cumulative evidence suggesting that under particular circumstances, food can also affect mental health as noted in the inborn error of metabolism called phenylketonuria. Where specific offending foods are removed from the diet in conditions such as phenylketonuria, remarkable benefits are noted in relation to behaviour and cognition. *Ergo*, science has a template for suggesting that a gut–brain axis exists and food is a potentially modifying variable. Such a template may also be pertinent to some autism; not only on the basis that various important inborn errors of metabolism may be over-represented in cases of autism<sup>(17)</sup> (including phenylketonuria) but that the interest in the GI tract in relation to autism similarly models a potential role for dietary factors in some instances.

Drawing on earlier research hinting at a role for the GI tract and diet in cases of schizophrenia spectrum disorders<sup>(18)</sup>, research focus has shifted to specific dietary elements as being potentially important to autism. Wheat or more specifically gluten, has received considerable research attention on the basis of the pharmacology of the protein and its breakdown metabolites and their similarity to other biologically-active agents<sup>(19)</sup>. The focus on opioid peptide metabolites has similarly 'pulled in' other foodstuffs such as milk and dairy products on the basis of their proposed similar chemical activity<sup>(20)</sup>.

Various studies have reported on the effects of removal of gluten and casein containing foods from the diets of people on the autism spectrum<sup>(15)</sup>. By no means a universal effect<sup>(21)</sup>, discussions have turned to the possibility that within the autisms there may be one or more phenotypes<sup>(12)</sup> sensitive to such dietary elements. Such a notion opens up the possibility of identifying potential best- and non-responders to dietary intervention impacting on some of the core and peripheral aspects of autism<sup>(22)</sup>.

There is still confusion about what specific elements may be at work when it comes to examining the effects (or not) of a gluten- and casein-free diet in relation to autism. Five key areas stand out in the research literature potentially pertinent to effects: (i) the biological activity and pharmacological effects of the specific foods; (ii) the role of enzyme function or conditions for enzyme functions acting on the metabolism of foods; (iii) altered intestinal barrier function as a means of any food-derived biological activity reaching the wider central nervous system; (iv) a role for immune function and specific responses to dietary elements; (v) a role for the collected gut microbiota.

### **Dietary elements as biologically active entities linked to autism?**

With the requirement for greater research inspection, the suggestion that the opioid-like qualities of peptide species derived from gluten and casein<sup>(19,20)</sup> may impact on the presentation of autism has a long history. The notion that there is overlap in the behaviours noted in situations of long-term opioid exposure (in animals and human subjects) and cases of autism provided a basis for early explanations of how such food elements might affect behaviour. The inclusion of other potentially important effects linking GI symptoms (e.g. constipation) and opioid-based drugs<sup>(23)</sup> also coincided with some of the functional bowel findings noted in autism<sup>(13)</sup>. Independent evidence citing the potential effectiveness of certain anti-opioid medication (naltrexone) in relation to facets of autism<sup>(24)</sup> and studies querying enzymatic function pertinent to gluten and casein protein metabolism<sup>(25)</sup> also added to the feasibility of an opioid-excess hypothesis of autism. Similarly, dietary interventions probably affecting gluten and casein intake but not exclusively labelled as gluten-free casein-free have also provided surrogate evidence for potential effects. The use of a ketogenic diet, high fat, low carbohydrate, in cases of autism for example, has some supporting evidence of effect<sup>(26)</sup>.

### **Intestinal barrier function(s) and autism (but not 'leaky gut')**

'Leaky gut' in the context of autism still invokes ridicule and charges of pseudo-science in some quarters. Despite increasing evidence implicating alterations to the permeability of the intestinal barrier in relation to various conditions<sup>(27)</sup> including autism<sup>(28,29)</sup>, the term remains contentious. Such a response is not helped by the implications that: (a) the intestinal barrier is an impenetrable barrier deflecting anything and everything away from contact with the wider central nervous system; (b) by labelling the gut as 'leaky', there is an oversimplification of the complex structure and workings of the intestinal barrier in relation to its large surface area and lack of uniformity when it comes to permeability.

It is perhaps therefore more accurate to use the term intestinal hyperpermeability to denote a more realistic scenario where appreciation for intestinal permeability exists; not least that typical GI permeability represents a key process in diverting energy (nutrition) from the digestion of dietary elements into wider circulation. The focus is therefore on atypical permeability and how this manifests in relation to autism.

As mentioned, there is evidence for intestinal hyperpermeability in cases of autism<sup>(28,29)</sup> based on both direct measurement and also as a function of other observations such as evidence of bacterial translocation<sup>(30)</sup>. The precise reason(s) for such a state are not yet fully understood but diet has been observed to be a potential factor; specifically the use of a gluten-free casein-free diet<sup>(28)</sup> mirroring research in relation to other labels<sup>(31)</sup>. The possibility of a direct effect of dietary elements, specifically gluten and casein metabolites, on gut barrier integrity provides an additional strand to the notion that such foods can affect some autism. Not only may opioid peptides originating from foods containing gluten and casein have potential direct pharmacological activity on the central nervous system (brain) but also they could be key moderators of the means to enter into general circulation. Such effects require further investigation. Specifically how such entities may impact on the enteric nervous system (i.e. within the GI tract) and their action on key barrier proteins such as zonulin<sup>(32)</sup>.

### **The gut-'bug'-brain-behaviour axis**

The collected bacteria and other species that populate the human GI tract has become big research business in recent years. Not a day seemingly goes by without a specific species or general measure of bacterial diversity being implicated in all-manner of conditions, labels and states. What is becoming clear from the science so far is that the functions of the gut microbiome do seem to be more diverse than merely aiding digestion or the production of nutrients. No better example of this extended role is evidenced by the notion of psychobiotics<sup>(33)</sup> denoting how elements of the gut microbiota may carry influence on aspects of human and animal behaviour and development. The production of peripheral serotonin in the GI tract by enterochromaffin cells as potentially being mediated by the gut microbiota represents one example of psychobiotics in action.

Still a research area in its infancy, autism (whether modelled in animals or studied directly) has provided some key information about a possible relationship between the gut microbiota and behaviour and/or development. Rodent studies, for example<sup>(34)</sup>, have linked behaviour, gut bacteria and intestinal permeability. Various human studies have detailed differences in gut bacterial constitution in relation to autism<sup>(35)</sup> based on both individual species and overall bacterial diversity. More preliminary data on how specific probiotics, bacterial species thought to confer some health advantage, may affect the presentation of autism<sup>(36)</sup> have also been published. Research on the potential effectiveness of

faecal microbiota transplant in relation to autism<sup>(37)</sup> has similarly been undertaken.

More investigations are required as to the importance of the gut microbiome in relation to autism. The mechanism of effect, from gut bacteria to behaviour, in particular requires further explanation<sup>(38)</sup> and how diet and other factors will influence gut bacterial populations for example. It is however, getting harder to discount the idea that the gut is truly a ‘thinking organ’ and, alongside producing various neurotransmitters and hormones, the cross-talk between gut bacteria and the central nervous system may be important for various labels/conditions/states including some cases of autism.

### Where next?

Research does not happen in a social or political vacuum. Autism is a prime example of this notion, as within the complexity and diversity of the label, various viewpoints exist on issues such as the gut–brain axis and the acceptability of interventions related to diet or other GI-affected issues. The question of ‘where next?’ therefore is not one simply driven by science but also an understanding of the wants and wishes of those on the spectrum and their significant others.

It is logical to assume that given the presence of GI issues in cases of autism (sometime severe and life-changing) moves to alleviate such issues should be accelerated. If by altering the pattern or severity of such GI issues corresponding positive changes are noted in behaviours linked to autism that negatively affect quality of life, this should be welcomed. The various processes already noted (dietary elements, intestinal barrier functions, gut microbiota) separately and cumulatively lend themselves to intervention. The use of artificial enzymes to aid digestive processes<sup>(39)</sup> represents one intervention avenue in addition to those mentioned in relation to the use of probiotics and/or faecal microbiota transplant. Dietary changes also remain a possibility in light of the evidence of effect (for some) already produced. Early findings in relation to the expression of the barrier protein zonulin in relation to autism<sup>(40)</sup> require replication and lend themselves to possible intervention.

To correct one generalisation already mentioned in this commentary, that all milk sources are chemically the same in terms of their release of opioid peptides during digestion<sup>(41)</sup>, other areas of intervention are also opening up. Studies highlighting short-term positive behavioural effects following the use of alternative mammalian milk sources (alternative to cow milk) in relation to autism<sup>(42)</sup> have offered potential evidence of effect. Taking into account the existing literature on how GI issues may be overrepresented when it comes to autism<sup>(13,14)</sup> the idea that not all cow milk may provoke the same GI issues<sup>(43)</sup> provides a platform for additional studies specifically in relation to the use of a1  $\beta$ -casein free milk (a2 milk) and autism<sup>(44)</sup>. Research is currently underway examining whether, under double-blind, placebo-controlled conditions, use of a2 milk might

impact on some of the core and peripheral behavioural presentations of autism<sup>(45)</sup>.

### Conclusions

The case for the diagnosis of autism reflecting a complex, diverse and rarely stand-alone condition has been proven beyond doubt. The idea that the brain, although central to the behavioural presentation of autism, is not the only organ important to autism is gaining scientific momentum. Within the diversity of autism, the plural autisms, the GI tract is being implicated in multiple cases potentially pointing to one or more autistic phenotypes being characterised by GI involvement. Evidence is accumulating to suggest that various facets of GI function may exert an important influence on the presentation of behaviours linked to autism. Interventions targeting adverse GI conditions in relation to autism may also show some promise in terms of positively affecting aspects of autism in light of a growing interest in a gut–brain–behaviour relationship.

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### Conflicts of Interest

None.

### Authorship

P. W. is the sole author of this paper.

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