

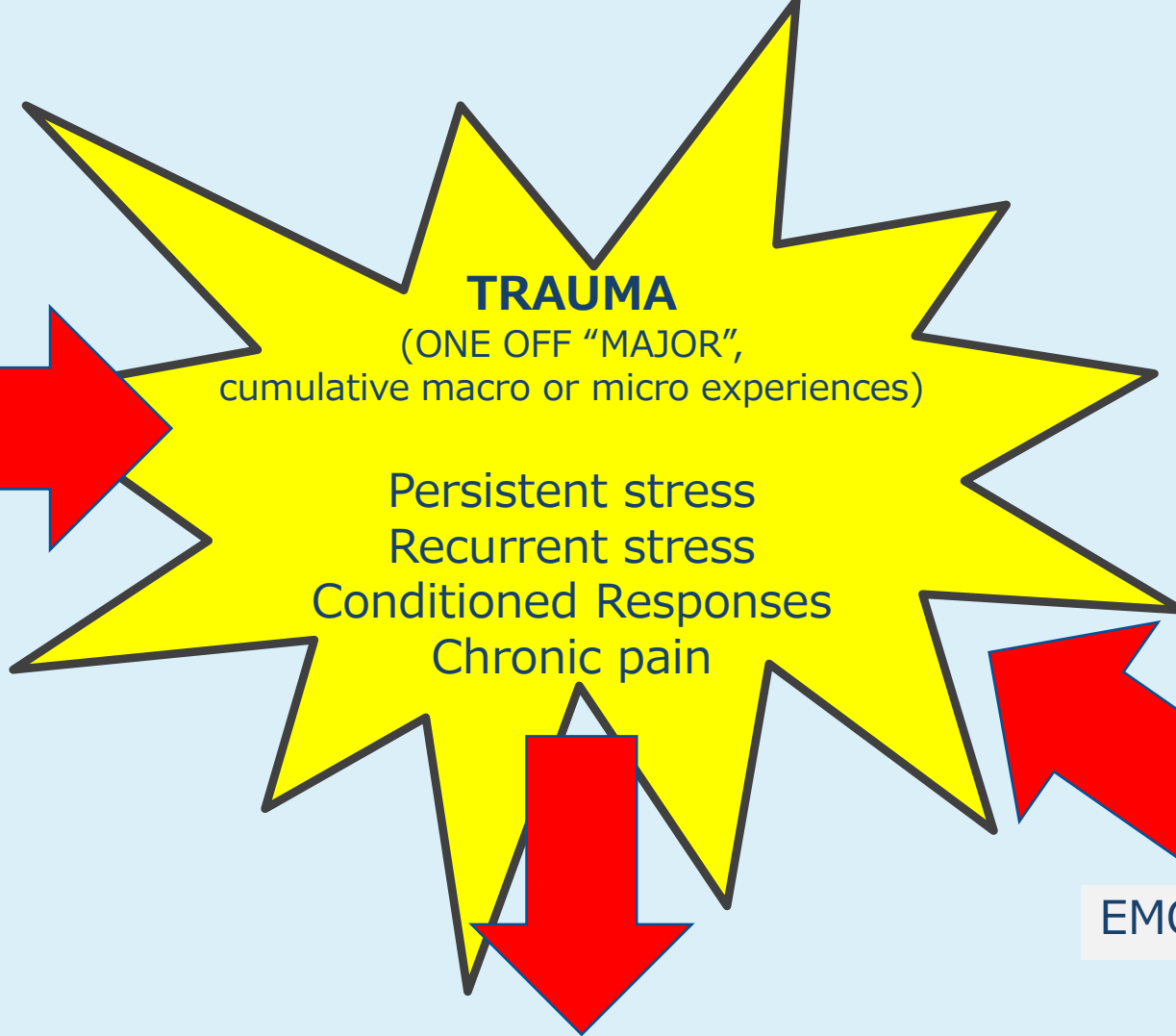
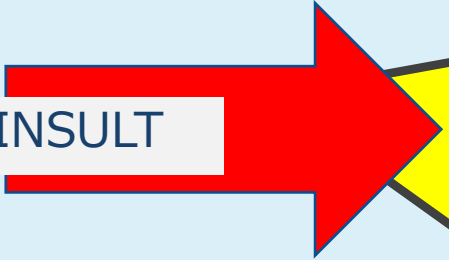


Getting to the guts of trauma

Dr Amber Batson MRCVS

Control the Meerkat Trauma Conference 2022

PHYSICAL INSULT

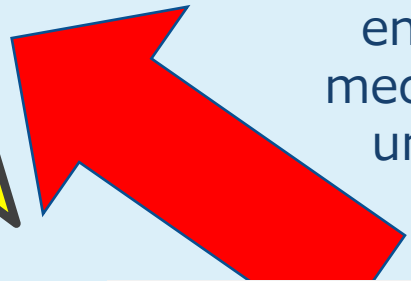


TRAUMA

(ONE OFF "MAJOR",
cumulative macro or micro experiences)

Persistent stress
Recurrent stress
Conditioned Responses
Chronic pain

EMOTIONAL INSULT



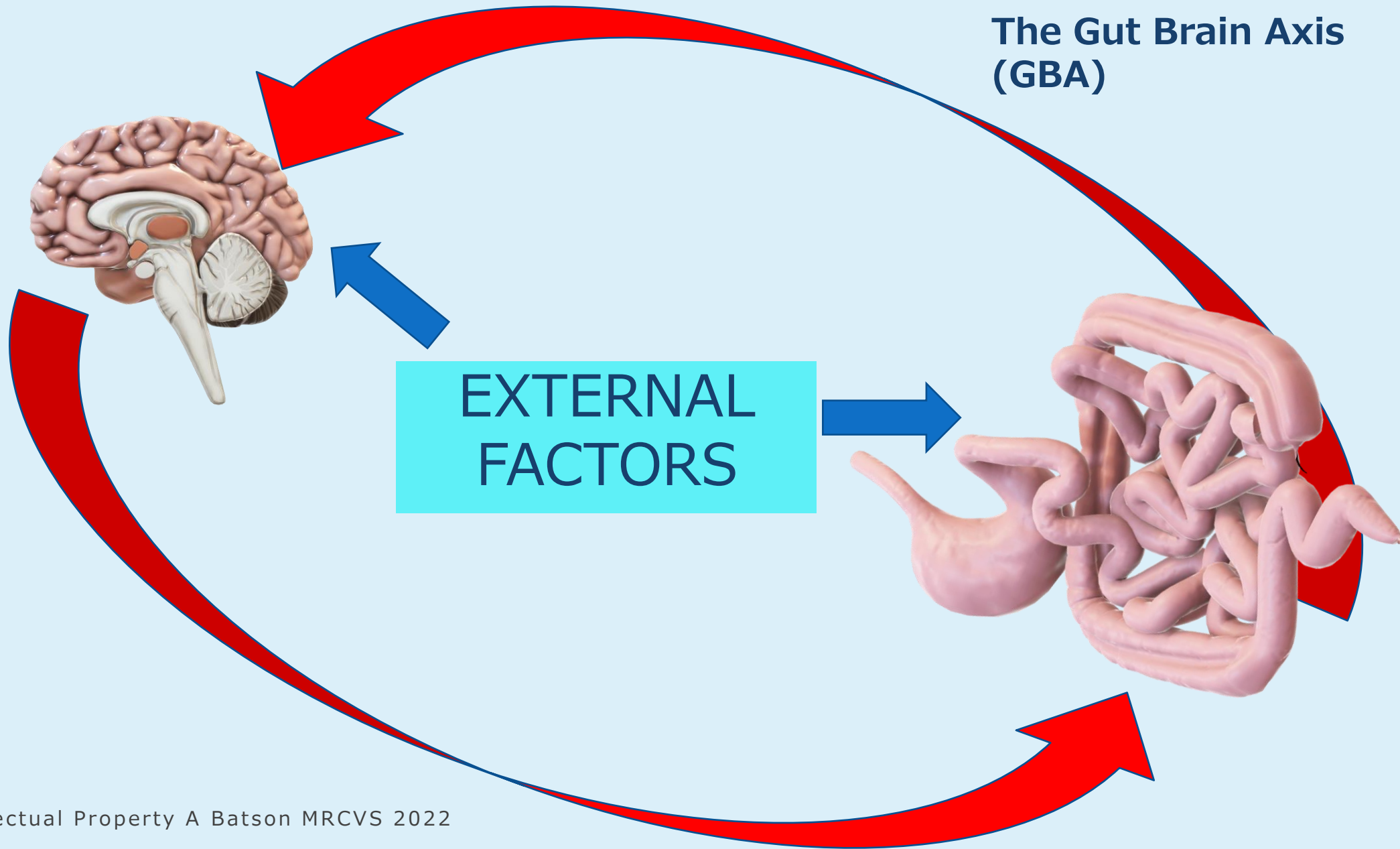
GUT CHANGE
Immune system compromise
Gut bug imbalance
Chronic gastroenteritis

For many who experience trauma, "coping mechanisms" (including protective physiology) develop.

We may label these as "behaviour problems" and seek to change them, but often they are an entrenched survival mechanism that needs understanding and supporting.

BRAIN – BODY CONNECTIONS

The Gut Brain Axis
(GBA)

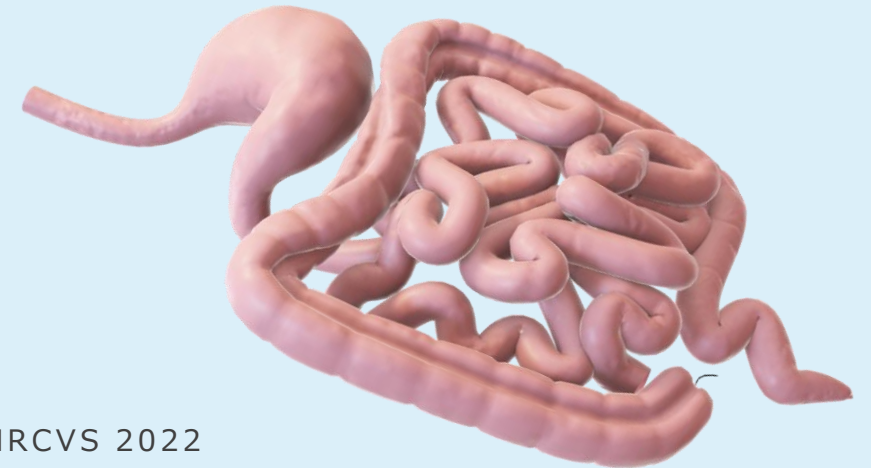


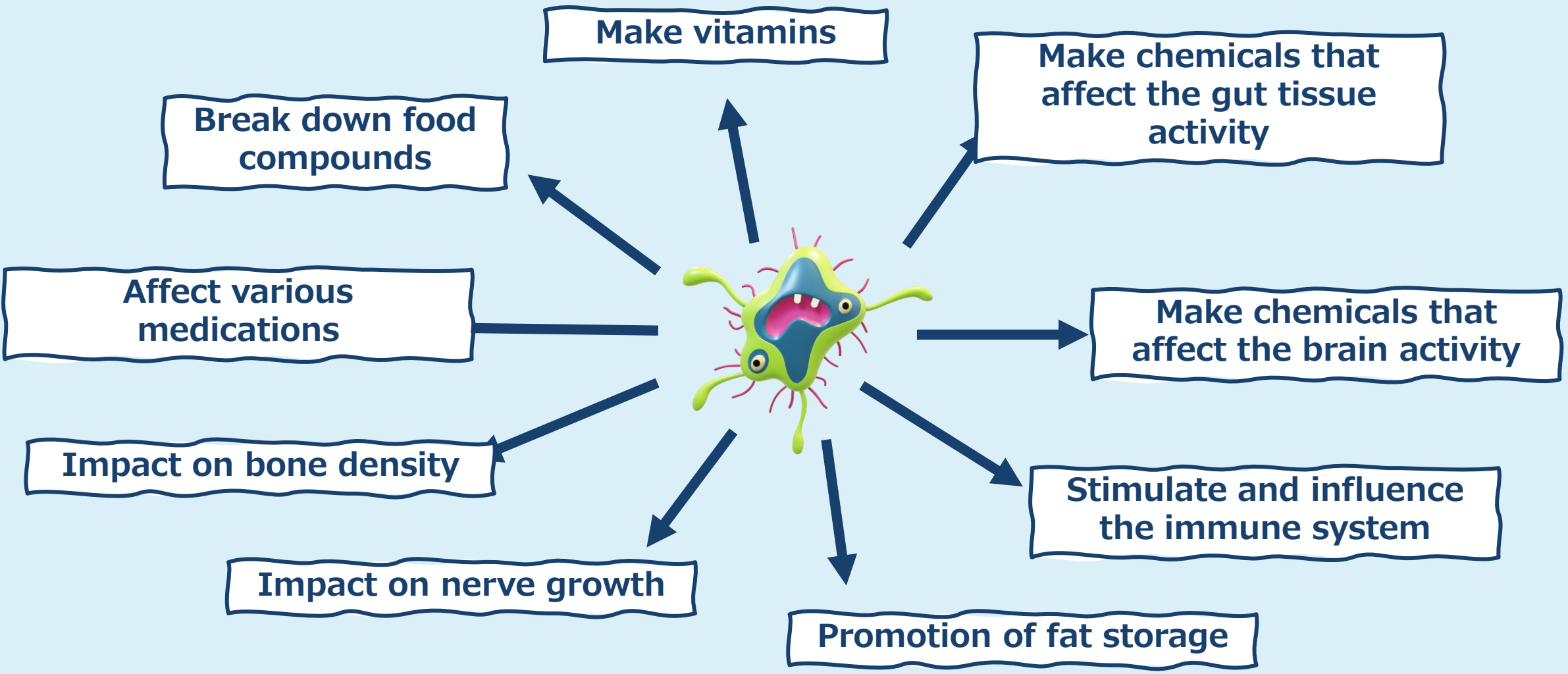
Getting to the guts of the matter...

What's all the fuss about those guts?!

Gut disease can affect a dog's behaviour in several ways...

- *Source of pain
- *Source of inflammation
- *Causing an imbalance of gut bugs (intestinal microbiota dysbiosis)
- *Affecting nutrient absorption
- *Affecting sugar levels





The living community of tiny organisms in the gut plays several important roles in a dog's health and homeostasis

THE BUGS HAVE IT !!

The bacteria in a dog's guts seem to influence the dog's behaviour & health in multiple ways

Relevance of trauma:

*Inflammatory states

How does stress affect the gut .. and then the brain

Long standing activation of stress pathways seem to result in a loss (reduction) of the tight junctions between gut cells.

This allows the bacteria normally trapped in the lumen to move in and around the gut cells, triggering an inflammatory response including LPS absorption.

LPS (lipopolysaccharides) are found on the outside of certain bacteria (gram negative). If these bacteria stay in the gut lumen, no problem, but leaky gut from persistent stress or other gut disease, can cause LPS to enter the blood stream and trigger an inflammatory response.

The inflammatory response can trigger changes in the blood brain barrier causing further stress pathway activation.

We are now recognising elevated inflammatory states as a risk factor for experiencing trauma

“However, inflammation itself may be a risk factor for developing PTSD, which would place individuals with IBD at greater risk for developing PTSD or IBD-related PTS after a traumatic event.”

Taft 2022

See Kelly et al 2015

THE BUGS HAVE IT !!

The bacteria in a dog's guts seem to influence the dog's behaviour & health in multiple ways

Relevance of trauma:

- *Inflammatory states
- *Other chemical production

Conversion of dietary tryptophan into serotonin vs indoles vs kynurenine

This influences behaviour because
*the amount of tryptophan left "unconverted" can reach the brain via the blood to make brain serotonin

*the gut serotonin can communicate to the brain via the vagal nerve

*the amount of kynurenine and indoles produced affects the immune system including inflammatory agents

Why does serotonin matter?

"For example, lower concentrations of serotonin in dorsal regions may disrupt limbic communication (specifically, between the amygdala and hippocampus) and in animal models, chronic exposure to stress and decreased 5HT transmission in the superior central nucleus can mitigate anxiolytic effects and promote memory encoding of associative learning.

As a result, individuals with PTSD who have lower levels of serotonin are more likely to experience classic symptoms of hypervigilance, impulsivity/aggression, and intrusive thoughts or flashbacks." Vuotto 2022

Serotonin activity is known to impact on pain perception, sleep, emotional regulation, aggressive tendencies, positive emotional states and appetite.

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Why does increased kynurenine matter?

A recent study showed that rats with higher stress induced KYNA levels had cognitive impairments, ultimately preventing their ability to discriminate certain fear contexts, with a greater potential for fear generalization. Klausing 2020

Kynurenine can be converted into KYNA or Quinolinic acid (this occurs in non neuronal cells in the brain).

Both act on NMDA receptors found on neurons, with KYNA having an inhibitory effect and Quinolinic acid having an excitatory effect.

In the presence of LPS inflammation, research has shown more kynurenine to shift into Quinolinic acid than KYNA. The results have been depressive like symptoms in those individuals. Remus 2016

“PTSD is frequently accompanied by cardiovascular disease (CVD), metabolic syndrome (MetS), diabetes mellitus type II (DMII), autoimmune diseases, early mortality, and perhaps even “accelerated biological aging,” defined as biological aging outpacing chronological aging.

This suggests that PTSD is a systemic, rather than solely a brain, disorder

Elevations of inflammatory markers are among the most widely replicated biological abnormalities in PTSD. It has even been suggested that PTSD is an “immunological disorder.”.....

Alterations in the gut microbiome and impairments in intestinal barrier function (IBF) may also be important in generating inflammatory responses, both peripherally and in the brain.

Psychological stress may impair IBF, allowing for translocation of bacterial components, thereby leading to inflammatory responses. These may also contribute to brain pathology and alterations in behavior via alterations of the tryptophan/kynurenine ratio, short chain fatty acid production and alterations in BBB permeability.

There have been no studies, to our knowledge, that specifically examined associations between the gut microbiome, impaired IBF, and inflammation in combat-related PTSD” Bersani et al 2020

THE BUGS HAVE IT !!

The bacteria in a dog's guts seem to influence the dog's behaviour & health in multiple ways

Relevance of trauma:

*Inflammatory states

*Other chemical production

*Production of GABA

*Production of dopamine

*Production of noradrenalin

*Production of SCFA's

GABA: anti-anxiety effects

Dopamine: affects metabolism (via thyroid), affects latent inhibition (decreased LI results in increased sensory experiences / even hypervigilance) ...

Short Chain Fatty Acids: have protective effects against stress induced gut related change. Impact on traumatic memory disorders perhaps through effects on non neuronal cells.

A gutsy reaction...

Recently published work in humans has shown that the microbiota plays a role in threat signalling...

The mechanism appears to be related to the amount of SCFA's produced and their interaction with the anterior insular – dorsal anterior cingulate cortices (dACC) ... but the full mechanism is not yet clear.

See

Hall, C.V., Harrison, B., Iyer, K., Savage, H., Zakrzewski, M., Simms, L.A., Radford-Smith, G., Moran, R.J. and Cocchi, L., 2021. Microbiota links to neural dynamics supporting threat processing. *bioRxiv*.

GUT HEALTH AND TRAUMA: THE OVERLAPS

“Our findings revealed that Single Prolonged Stress -model rats, exhibited fear and anxiety-like behaviors, as well as changes in levels of neurotransmitters such as 5-HT, DA, and NE. Additionally, SPS-model rats showed changes in the diversity and structure of gut microbiota. Based on the experimental results, we speculate that Firmicutes, Bacteroidetes, Cyanobacteria and Proteobacteria are most relevant to the development of PTSD in rats.”

“Regarding neurotransmitters, the prefrontal cortex is a considerable brain region for regulating emotions and is involved in the brain’s response to stress. Dysregulation of neurotransmitters such as 5-HT, NE, and DA is reportedly closely associated with PTSD, and DA is closely associated with the conditioned fear response. Furthermore, 5-HT is involved in behavioral inhibition, and its abnormalities can induce persistent fear, irritability, and aggressive fighting behaviors. Wilson et al demonstrated decreased 5-HT and increased DA and NE content in the hippocampus and prefrontal cortex of PTSD model rats, and increased NE activity is closely associated with PTSD symptom severity. In this study, 5-HT content in the brain was decreased in the rats model of SPS, suggesting that they were in a hyper-excited state, while the increased DA and NE content suggested that the body was excited but unable to create pleasant sensory feedback.” From Zhou et al 2020

All this new research, what does it mean for dogs who have experienced trauma?

Several pieces of research have looked at gut bugs, their “products” and the impact on behaviour, although it is only a start and none specifically looking at trauma as yet

“our study supports the intriguing opportunity that different behavioral phenotypes in dogs associate with peculiar Gut Microbiome (GM) layouts. Particularly, aggressive dogs possess dysbiotic GM configuration” Mondo et al 2020

Also in 2020 Mondo demonstrated a different gut bug population in German Shepherd dogs compared to other breeds / mixed breeds (very small study) and found similarities between this unique gut bug population and that of humans with depression.

“Although sample size limits this study, our findings indicate that gut microorganisms are linked to dog aggression and point to an aggression-associated physiological state that interacts with the gut microbiome.” Kirchoff 2019

A recent study suggested the use of a specific probiotic *Lactiplantibacillus plantarum* may alleviate some behaviours (separation anxiety & aggression?) in dogs Yeh et al 2022

See also Pereira 2021. Dogs’ microbiome from tip to toe.
& Ziese et al 2021 A detailed review of the canine (& feline) microbiome

Because of the complicated interplay between the gut bugs (intestinal microbiome), their “products” (metabolome) and the immune system, chemical messengers and the brain, normal digestive function and gut health are likely to play an essential role in many elements of health and behaviour.

There are multiple causes of chronic gut disease in the dog:

- *Types of chronic inflammatory enteropathy (often called IBD) which can be food responsive (FRD) antibiotic responsive (ARD) or steroid responsive (SRD)

- *Bacterial infection eg Campylobacter, Salmonella

- *Viral infection eg Parvo virus,

- *Parasitic infection eg Giardia

- *Neoplasia eg lymphoma

- *Secondary enteropathy eg pancreatic disease, kidney disease, heart disease

See Volkmann et al 2017

Where a dog with suspected trauma history has known gut disease we should do our best to find & treat the underlying cause

Obvious symptoms of gut disease:

Diarrhoea or constipation
Intermittent loose faeces
Colitis
Blood in faeces
Excessive flatulence / belching
Vomiting

Less obvious symptoms of gut disease:

Skin disease (see Harvey 2019, Craig 2016)
Appetite issues
Coprophagia
Pica
Epilepsy
Signs of intermittent pain
Behavioural change

What can we measure?

Faecal cultures / assessment
Faecal microbiome (but not bug output as yet)
Bloods to look for underlying causes, inflammatory states,
small intestinal function (cobalamin / folate, proteins)
Thickness of intestinal wall via ultrasound
Lining of stomach, upper SI and distal colon via endoscopy
Response to trials (dietary and medical)

The Recipe for Good Gut Health

It starts before you are born:

Stress in mum during pregnancy, impacts on her own and therefore the foetal microbiome , as well as impacting on the development and sensitivity of the stress pathways and even sensitivity of pain pathways. See Tochtani 2016, DeGroot 2016, O'Connor 2021 as some examples.

Then:

Vaginal versus caesarean births

Mum's milk versus formula,
early weaning (loss of milk, type and introduction of diet), diet

Antibiotics

Anaesthetics

Stress

Social experiences

Sleep

Exercise

Enrichment (life, versus short lived activities)

Trauma and the gut: the two way street

“In summary, this proof of concept study suggests that ELA [Early Life Adversity] in the form of institutional rearing during infancy may be associated with gut microbiome differences in adolescence, years after the adversity had ended.

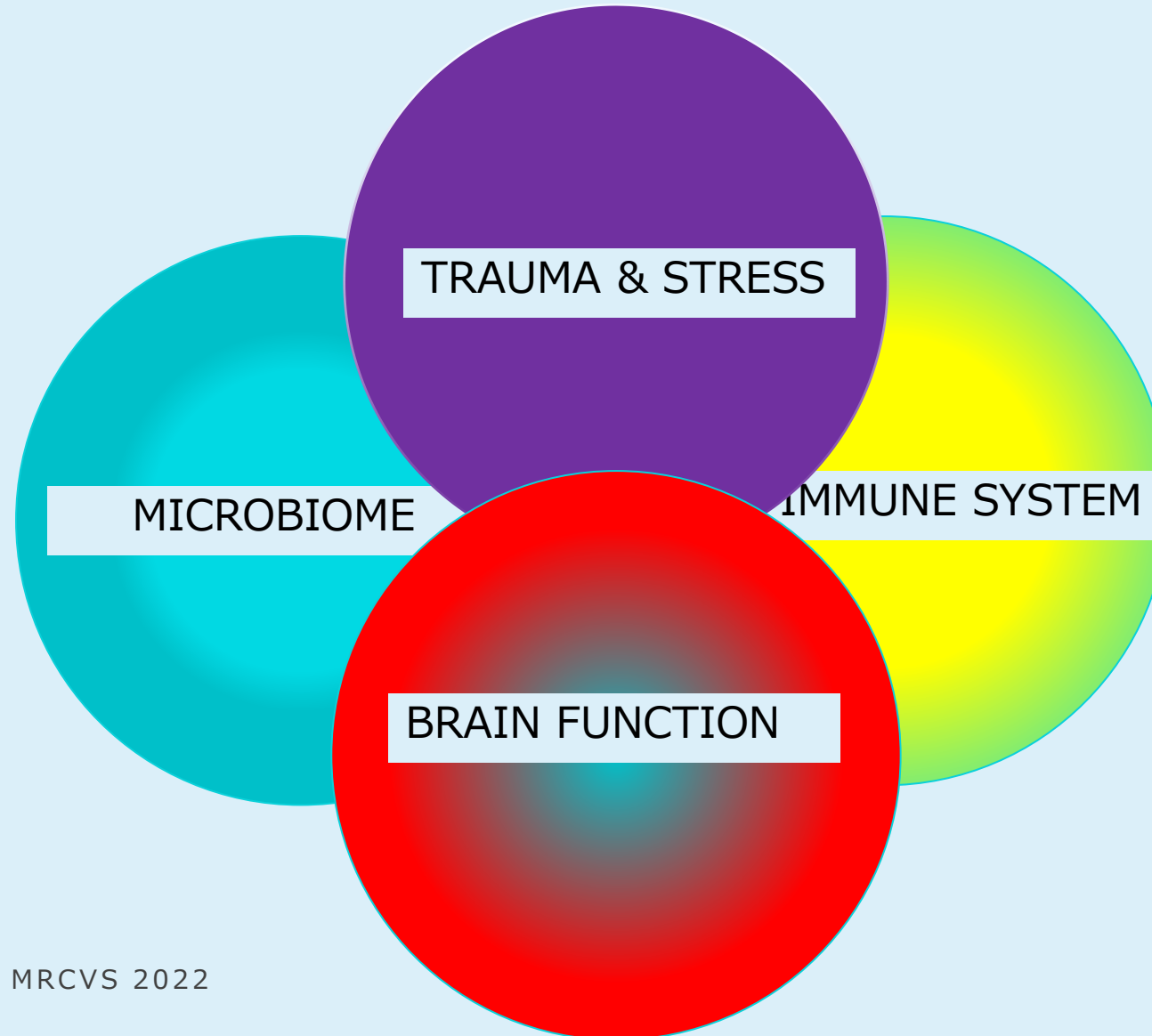
There was no evidence that these differences were due to current diet or current health. Rather, they were statistically associated with alterations in the immune system and the presence of CMV, viral antibodies to which nearly all of the PI [previously institutionalised] youth and few of the COMP [comparison] exhibited.

Previous work on ELA has emphasized psychological processes and stress responses as the pathways through which early adversity “gets-under-the-skin” to influence neurobehavioral development. These data argue that we need to pay greater attention to other pathways through which adversity may be transduced into physical and mental health trajectories. Of those other pathways the immune-microbiota pathway is clearly worthy of exploration.”

From Reid 2021

See also Stress gets into the belly: Early life stress and the gut microbiome Hantsoo 2021

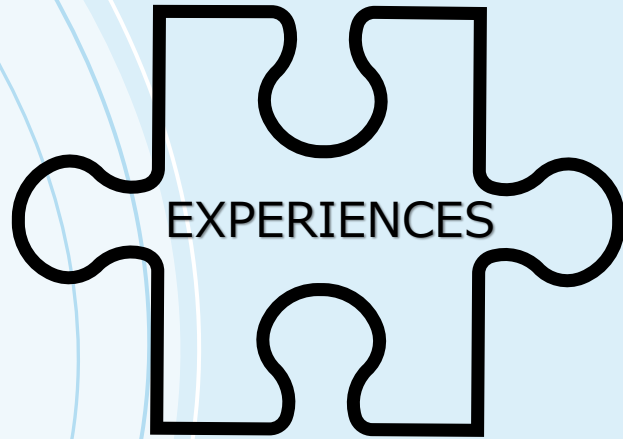
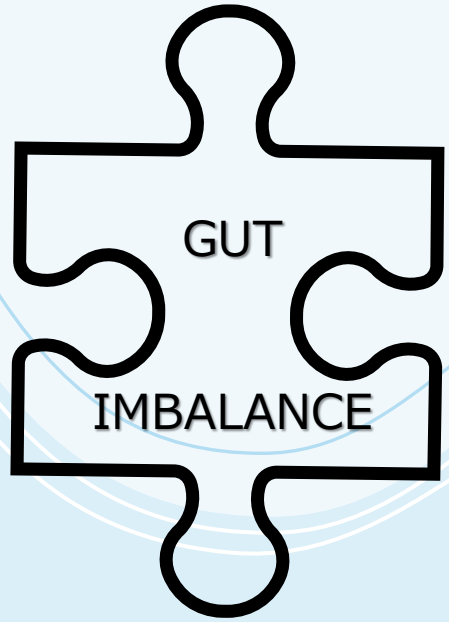
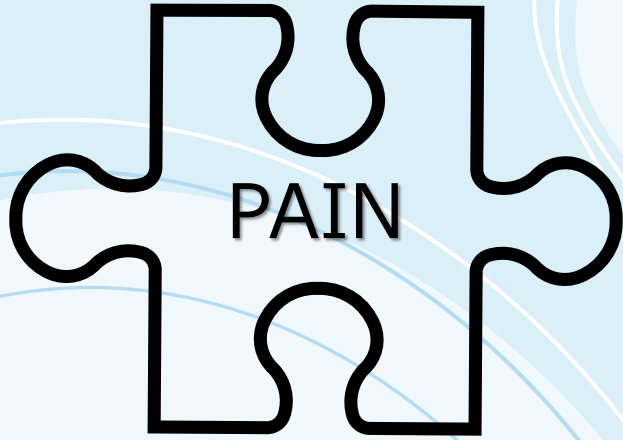
The huge overlap between trauma & stress, the microbiome, the immune system and the way the brain then functions to “drive” observable behaviour, means we simply cannot look at modifying post trauma / post stress behaviours by aiming to change the behaviour alone.



Diseases that manifest as a result of gut/body/brain imbalance

or diseases that cause gut/body/brain imbalance,

need to be assessed from an “integrated” brain/body/bug/environment perspective if we are to truly effect change and “stability” in the individual.



Making it all better ...

Firstly, we must address any co-existing, contributing factors such as

- *Pain
- *Disease
- *Intestinal dysbiosis

- *Persistent, repeated stress

Remove triggers, overshadow triggers,
review lifestyle and expectations

Provide safe space, safe relationships, positive social support

- *Poor sleep

Sleep is a better medicine than drugs ??

“Sleep and posttraumatic stress disorder (PTSD) have a complex relationship, with some studies showing that disrupted sleep is associated with subsequent development of PTSD.”

From DeViva et al 2021

Sleep reductions have been reported to increase systemic inflammation which can further increase many of the brain, immune and gut microbiota changes occurring in post trauma responses, as well as sleep reductions affecting cognitive appraisal, negatively affecting mood and influencing pain perception.

Improving sleep amounts and quality has real potential to reduce some of these factors.

Letting sleeping dogs lie.....

*Polyphasic (across 24 hours)

*Social

*Warmth / comfort

*Choice including space and elevation

Details on canine sleep is outside the scope of this presentation. Some useful references include

Bollo et al 2020

Kinsman et al 2020

Kortikaas et al 2020

Mondino et al 2021

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Remove triggers, overshadow triggers,
review lifestyle and expectations

Provide safe space, safe relationships, positive social support

- *Poor sleep
- *Inappropriate exercise patterns (limit fast sprints, anaerobic exercise,
increase slower aerobic activities)
- *Diet
- *Enrichment (using all 8 senses! And based on the canine ethogram)

Making it all better ...

“These results [in piglets] suggest that creating a physically and socially enriched environment in early life can modify caecal microbiota structure and animal response after weaning probably by means of diminishing social stress response.” Saladrigas-Garcia 2021

Replicated in hens, mice and rabbits to date

A recently publication on housed rabbits, showed that environmental enrichment reduced measurable stress, and resulted in a gut microbiota characteristic of healthy rabbits compared to that of rabbits in non enriched, conventional housing. See Feng et al 2022

Something a bit fishy ?

A variety of supplements / nutraceuticals have been considered with respect to their ability to reduce anxiety/ fear / stress in dogs.

Growing interest into the potential for SCFAs (short chain fatty acids) as a benefit to the gut bugs is suggesting that the fatty acids in fish oils may have stress reducing effects.

More information can be found in

Landsberg et al 2015

Su et al 2018

Titeux et al 2021

To bug or not to bug? With which bugs... That is the question!!

Use of pre or probiotics:

We just don't have enough answers just yet ...

Broadspectrum probiotic ?? See Kim et al 2021 Jang et al 2021

And a great recent review of the issues by Lee 2022

Which bugs?

How many?

In ratio to ?

The bugs themselves or what they produce?

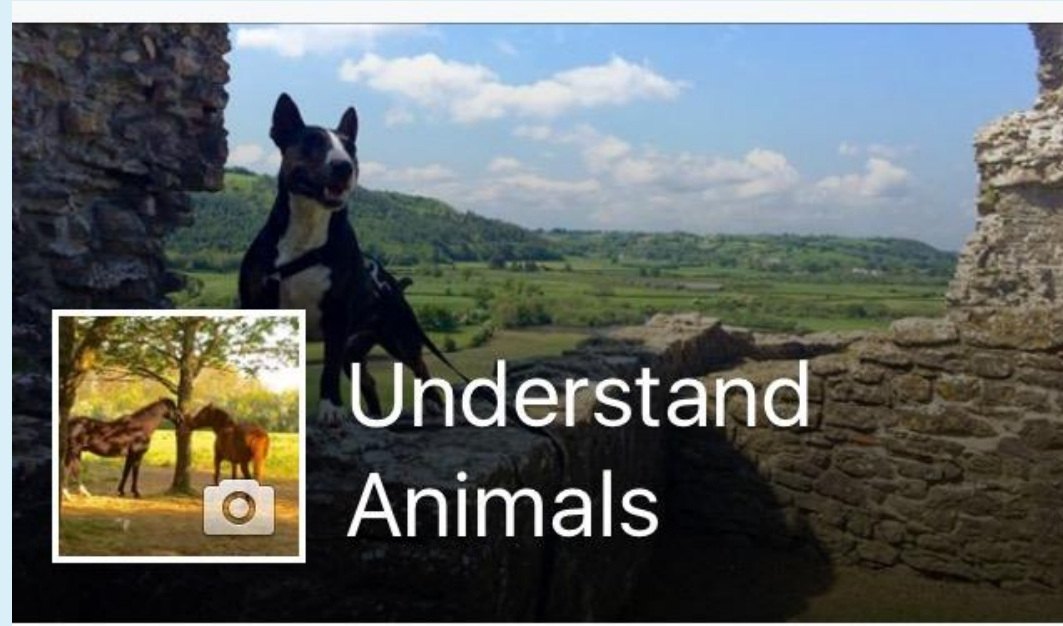
Can their "products" be as effective?

Prebiotics – food for the existing bugs

Probiotics – bugs

Postbiotics – what the bugs make

We're just not quite there yet
But it is fascinating stuff



Thank you for listening

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