Brain-Gut Connection
Nutritional and Digestive factors in ADHD and Autism

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Major causal factors in Developmental and Psychiatric disorders and modern diseases?
1. Genetic predispositions (Polyphormisms)
2. Modern diet compared to evolutionary hunter gatherer diet
   - Reduced FISH (Omega 3 EPA/DHA) consumption
   - Increased Omega 6 and trans-fatty acid consumption
   - Dairy, sugar, refined carbohydrates and gluten
   - Micronutrient deficiencies in our soil. e.g. Zinc and selenium
   - Chemical fertilisers, food refining and processing
   - Inadequate antioxidants and nutrients in processed foods
3. Toxic chemicals in the environment and food chain
   - Preservatives, additives, colourings and antibiotics in food
   - Use of antibiotics and toxic chemicals
   - The use of toxic heavy metals which in nature, are sealed in rocks and kept buried.
4. Viruses, detrimental fungi and bacteria

Human development

Nutrigenomics and Health
- Inuit people (Eskimos) on traditional diet.
- Rural and coastal Japanese on traditional diet.
- Mediterranean Islanders on traditional diet.
- Same people on western diet develop all modern diseases, within one generation.
- E.g. Inuits on western diet now have 5 times cardiovascular disease rate of Canadians

The cell body

Cell plasma membrane

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Dry volume of brain
• 70% - lipids (fats)
• 13% - AA (O6)
• 25% - DHA (O3)
• 10% - EPA (O3)

EPA and DHA are Omega 3 Fatty Acids from oily fish e.g. salmon.

Almost all psychiatric disorders and modern diseases have been linked to deficits in these two Omega 3 fatty acids and micronutrients necessary for their metabolism.

Prof. Andrew Stoll - Harvard University Medical Centre "The Omega 3 Connection"

DHA concentrates in synapses and modulates the synthesis, transport and release of the brain's messenger chemicals: Serotonin, Dopamine and Norepinephrine.


1999 Dietary estimates of EFAs
Comparison of total Omega 3 to Omega 6 between paleolithic and modern diet

(Eaton, NIH Workshop on essentiality of EFAs, 1999, Sinclair 2001)

Red cell % DHA in Autism, ADHD and normal healthy controls


Omega 3 and Dopamine
Delion and colleagues compared rats on a diet deficient in omega-3 to rats on a diet with adequate omega-3.
They found lower density of dopamine D2 receptors and lower dopamine levels in the brain of omega-3 deprived group.
The non-deprived rats had a higher ratio of omega-3 to omega-6 in their brain cell membranes.

Increasing omega-3 in the diet of these DHA-deprived rats resulted in increased dopamine receptor density as well as increased dopamine levels in their cerebral cortex.

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Gut/Brain interactions

MINDD March 2009- Underlying causes

Omega 3, ADHD and Autism

Several studies have found low Omega 3 fatty acids in children with ADHD, Dyslexia and Autism.


Bekaroglu, M., Y. Aslan, et al. (1996). "Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder."


Zinc is involved in 100s of biochemical pathways

• The most common micronutrient deficiency in ADHD
• Zinc is involved in 100s of biochemical pathways
• Australian Soil is deficient in Zinc
• Zinc is therefore lacking in our Australian diet


Magnesium Deficiency

• The next most common micronutrient deficiency in ADHD
• Magnesium and calcium are used up to buffer the chronic systemic acidity caused by stress and from an acid-producing diet high in dairy and grains.

(?) Who designed the Healthy Eating Food Pyramid?

• Magnesium deficiency and autism


Baugham, J A., Jr. (2000). "Dopamine transporter density in patients with ADHD."


Role of EFAs in Aetiology of Irritable Bowel Syndrome (IBS)

• Omega 3 EFAs provide a potential therapy for IBS and inflammatory bowel disease.

• "...there is also recent evidence that abnormalities in fatty acid profiles... may be a key component in the multifactorial aetiology of inflammatory bowel disease."

• "Such abnormalities are likely to be the result of a genetic susceptibility to the changing ratios of Omega-3:Omega-6 fatty acids in western diets."

Kils, S., Windsor, A., Knight, S. Clinical and Experimental Immunology 2005. 1265-2249.

ADHD has been associated with low Dopamine and Low Dopamine D2 receptor density


Baugham, J A., Jr. (2000). "Dopamine transporter density in patients with ADHD."


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Intestinal Dysbiosis

- State of disordered bacteria in the gut that can cause disease
- It is due to an overgrowth of detrimental gut bacteria at the expense of beneficial gut bacteria.
- Microbial balance is the key factor that determines whether substances in the intestine are converted into compounds that are beneficial or detrimental to the host.


Lipopolysaccharide (LPS)

- LPS is a major component of the outer lipid membrane of Gram-negative bacteria. e.g. E-Coli
- LPS is a toxin which induces a strong response from animal and human immune systems.
- LPS promote the secretion of pro-inflammatory cytokines in many cell types.

Lipopolysaccharide and cognitive function.

- LPS induces cytokine inflammation in the brain associated with negative changes in cognitive function.
- In animal studies, these changes are associated with impairment in learning and memory.
- Rats treated with EPA, GLA or both had increases in protective anti-inflammatory cytokines


Lipopolysaccharide and depression

Several studies suggest that increased production of pro-inflammatory LPS induced cytokines may play a role in depressive disorders.


Lipopolysaccharide and Hippocampal Neurogenesis

- New hippocampal neurons are continuously generated in the brain.
- Findings suggest that LPS-induced brain inflammation results in suppression of hippocampal cell generation.
- This impairs learning and memory and contributes to cognitive dysfunction.


Lipopolysaccharides and Metallothioneins

- Zinc is an essential micronutrient for the normal function of the brain
- Zinc is involved in neurotransmitter synthesis and brain cell membrane metabolism.
- When LPS elicited an inflammatory response, mice low in zinc had significantly less brain metallothioneins (proteins that control the movement of metals in and out of cells)
- Metallothioneins provide protection against heavy metal toxicity, and provide protection against oxidative stress.

Lipopolysaccharides and HPA axis
- Injection of LPS caused a dramatic increase in concentrations of noradrenaline, abnormal heartbeats, elevated corticosterone levels, and sickness behavior.
- The increase in noradrenaline levels may participate in hypothalamic-pituitary-adrenocortical (HPA) axis activation. (Causing anxiety and agitation)
- LPS resulted in highly specific changes in brain neurotransmission, affecting circuits involved in autonomic, hormonal, and behavioral regulation.


Impact of Intestinal Dysbiosis on Amino acids and Amines.
- Gram +ve bacteria: Enterococcus, Streptococcus, Staphylococcus, Clostridia, Bifidobacteria live and reproduce best in acidic gut conditions
- Under these acidic conditions they produce less amino acids and more amines.
- They also produce antigens that mimic cells in the body and the brain causing autoimmune disorders
- They are only a problem when there is an open portal e.g. leaky gut or ear, nose or throat infection or wound allowing their antigens to enter the body.

Amines and Brain Function
- Amines: e.g. tyramine, histamine, phenylethylamine, exist in some foods and are also formed by the breakdown of proteins by some gut bacteria.
- There are receptors for amines amongst the brain neurotransmitter receptors.
- High amine levels scramble neurotransmission.
- Amines can affect mental functioning, blood pressure, body temperature, and other bodily processes.
- Amines can cause headaches, foggy head, poor focus, fatigue, muscle aches and pain.

Anxiety and depression from amines
- Certain gram +ve bacteria, Bifidobacteria, Streptococcus, clostridium and Enterococcus produce large amounts of trace amines under acidic conditions.
- Trace amine receptors are found amongst Serotonin, Norepinephrine and Dopamine receptors in the brain.
- Food allergies associated with increases in trace amines have been proposed in the aetiology of depression

Irritable Bowel Syndrome (IBS)
- Variable stool consistency and frequency
- Constipation - loose stools - diarrhea
- Rarely well-formed stools
- Recurrent lower abdominal pains
- Bloating, flatulence (excess wind)
- Food sensitivities
- Leaky GUT and inflammation
- Tiredness, fatigue, Irritability, labile temper
- Depression and cognitive dysfunction
- Many Psych. patients, ADHD and Most Autistic children have Irritable Bowel Syndrome

Gut Bacteria and IBS
- The normal response to bacterial infection, such as vomiting and diarrhea, is protective and beneficial.
- However, in about 10% of patients symptoms persist and reflect the development of post-infective IBS, which may persist for many years.

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IBS and Psychiatric disorders

- Several studies have shown that up to 70% to 90% of patients with IBS who seek treatment have psychiatric comorbidity, most notably mood and anxiety disorders.

- Recent studies have shown a high prevalence of IBS in psychiatric patients who seek treatment, with a prevalence of:
  - 19% in schizophrenia,
  - 29% in major depression,
  - 46% in panic disorder.


GUT Immunity

Peyer's patches contain specialized cells called M cells which sample antigen directly from the lumen and deliver it to antigen-presenting cells. B cells and memory cells are stimulated upon encountering antigens in Peyer's patches. These cells then pass to the mesenteric lymph nodes where the immune response is amplified. Activated lymphocytes pass into the bloodstream and travel to the gut where they carry out their final effector functions.

Leaky Gut

Intestinal Bacteria and Autism

- Patients with autism usually present with multiple intestinal symptoms including:
  - chronic diarrhea,
  - flatulence,
  - abdominal discomfort, and bloating
  - Aetiology most likely due to dietary changes, antibiotics, preservatives...
  - Development of autistic symptoms has been implicated to an antibiotic related abnormal gastrointestinal microbial flora

Horvath K. Pediatr. 1999

Intestinal Permeability in patients with autism:

- Altered intestinal permeability was found in 43% of autistic patients.

- Found mucosal damage of the gastrointestinal tract resulting in increased absorption of microbial macromolecules and peptides through leaky gut.

- followed by the expression of 'regressive' behaviours and/or developmental disorders


Faecal bacteria in patients with Autism (n=81)

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Faecal bacteria in some patients

<table>
<thead>
<tr>
<th>% Distribution</th>
<th>Healthy subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

Aerobes

The importance of *E.coli* metabolites in human metabolism

- *E.coli* produces chorismate
  - Chorismate is the precursor for
    - 4-aminobenzoate >>>>> folic acid
    - 4-OH-benzoate >>>> ubiquinol (CoQ10)
    - anthranilate >>>> tryptophan
    - Prephenate >>>> tyrosine, phenyalanine
    - isochorismate >>>> menaquinone (Vit K)

Relationship between Tryptophan producing organisms, intestinal reflexes and Serotonin

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**E.coli**

Tryptophan

5 Hydroxy Tryptophan

Serotonin

Stimulates peristaltic and secretory reflexes of the GUT

Brain (feel good) Neurotransmitter

Tryptophan Levels in Autistic Children

- Plasma concentrations of tryptophan in autistic patients were found to be low
  - Croonenberghs, 2000; D’Eufemia, 1995
- Tryptophan depletion led to a significant increase in behaviors such as whirling, flapping, pacing, banging and hitting self, rocking, and toe walking
  - McDougle, 1996

Methylation dysfunction in Autism

- Children with Autism have been found to have dysfunctional methylation and detoxification pathways.
- They have Less Methionine, less SAME, Less Homocysteine and less Glutathione

St James, J. et al. Am Jnl of Nutrition 2004

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Methylation dysfunction

- Methylation is needed for:
  - Neurotransmitter function,
  - Cellular function,
  - Myelination of nerve cells,
  - Histamine modulation,
  - Cellular energy transfer.

- Deficits caused by:
  - Genetic polymorphisms,
  - Selective diets and poor absorption of Vit B12, B6, folic acid, selenium and methionine.

Sulfation

- A process for detoxification which is inhibited by oxidative stress, inflammation, and poor absorption of sulfate.

- Abnormal sulfation is implicated in many aspects of autism. Namely:
  - Leaky gut
  - Neurotransmitter dysfunction
  - Detoxification abnormalities.
  - Glutathione is needed to bond & eliminate heavy metals.
  - Glutathione is synthesized from three amino acids: cysteine, glutamic acid and glycine.

Transulfuration

- A process whereby homocysteine and P5P, an active form of B6 produces cysteine.
- Cysteine serves as a source of sulfate.
- Cysteine produces taurine needed to produce bile salts.
- Cysteine produces metallothioneins, regulatory proteins needed for gene expression, metabolism of metals and cellular adaptation to stress.

Oxidative stress and Glutathione

Glutathione is a major free radical scavenger, the only endogenous antioxidant produced by the body, protecting cells against oxidative stress.

Major Route of Mercury Excretion:
- Glutathione binds to mercury molecules and excretes them in urine and bile.

Protein redox status:
- Glutathione prevents the oxidation of cysteine residues involved in the functional inactivation of proteins.

ATP production and mitochondrial integrity:
- Protects mitochondrial membrane integrity (mitochondria are minute organisms that live in our cells and provide us with energy).

Integrity of gut epithelium:
- Glutathione depletion is associated with degeneration of mucosal villi and increased gut permeability.

Normal T cell subsets and immune function:
- Responsible for Normal T helper cell maturation in the thymus. T cells identify antigens so that immune killer cells can attack and destroy them.

Gluten Free Casein Free Diet

- GFCF (GFDF) diet often results in dramatic improvement of symptoms of ASD, often followed by a plateau/slowed changes.
- GFCF diet mandatory for treatment of Autism.


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Gluten Free Casein Free Diet

- Autism Research Institute Survey of Parent Ratings of Treatment Efficacy:
- Casein Free: 49% reported improvements
- Gluten Free: 48% reported improvements
- Gluten and Casein Free: 65%

Current Opinion in Paediatrics

“Given the high prevalence of ADHD with co-morbid psychiatric disorders, stimulants cannot be effectively used for all children with ADHD...

...parents interested in non-pharmacologic treatment can pursue the use of complementary and alternative therapy.

The therapy most promising by recent clinical trials appears to be EEG Biofeedback.”


Brainwave activity

- Delta Sleep 1-3Hz
- Theta Drowsy, tuned off 4-7Hz
- Alpha Awake and alert 8-12Hz
- Beta Actively thinking 13-25Hz

Theta = high (poor concentration, tuned off)
Beta
Theta = low (focused, active processing)
Beta

High Theta/Beta ratio in ADHD/Autism

We directly shape EEG patterns by repetitively rewarding appropriate ones and ignoring inappropriate ones

Since EEG patterns are related to behaviours, normalising EEG patterns normalises behaviours

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Rationale for Neurotherapy

- We know that 90% of ADHD children have high theta/beta ratios compared to non-ADHD ones.
- Operant conditioning of the EEG to reduce Theta and increase Beta
- This normalises QEEG patterns and improves symptoms of ADHD.
  (Lubar & Lubar, 1984; Lubar, 1991; Tansey, 1991; Thompson & Thompson 1997; Rosister and Lavaque, 1995; Rosister, 2004).

Large multi-centre study

- 1089 subjects (726 children, 324 females, 186 with ADHD or ADD diagnoses) underwent twenty or more sessions of Neurotherapy
- Subjects were evaluated before and after Neurotherapy using a computer administered Test of Variables of Attention (TOVA)
- Neurotherapy produced significant improvement in concentration, attentiveness, impulse control, and response variability in eighty-five percent of those subjects.
- Neurofeedback training is effective in remediation of attentional dysfunction.
  Kaiser and Othmer, 2000

Neurotherapy v/s Ritalin (1)

- Neurotherapy group of 23 subjects
- Stimulant group, also of 23 subjects, matched by age, IQ, gender and diagnosis.
- 20 sessions of Neurotherapy.
- The Test of Variables of Attention (TOVA) was administered pre and post treatment.
- Both groups improved significantly TOVA measures of attention, impulse control, speed of processing, and distractibility
- The groups did not differ from each other on TOVA change scores.
- Conclusion Neurotherapy is an effective alternative to Ritalin stimulant medication.
  (Rosister & La Vaque, 1995).

Neurotherapy v/s Ritalin (2)

- 22 children (8 to 12 years) with ADHD received Neurotherapy to enhance SMR and/or beta activity and suppress theta activity, over a period of 10 weeks.
- The control group of 11 children matched by age and sex were optimally medicated with methylphenidate (Ritalin).
- IQ test, T.O.V.A, paper-pencil-test (d2) and IOWA Conners Behavior Rating Scales were administered pre and post treatment.
- The Ritalin and Neurotherapy conditions showed comparable and significant improvements in attention and concentration.
- Gains from Neurotherapy are permanent, while the gains in the medication group are dependant on continuation of medication.
  (Fuchs, 1998)
Neurotherapy v/s Ritalin (3)
- 100 children with ADHD, ages 6-19, participated in a one-year, multimodal, outpatient program that included Ritalin, parent counselling and academic support at school.
- 51 of the children also received Neurotherapy.
- Pre and Post-treatment assessments were conducted both while on and off Ritalin.
- Significant improvements were noted when all participants were tested while on Ritalin.
- However, only the Neurotherapy group sustained these gains when tested while off Ritalin.
- Only children who had received Neurotherapy had reductions in theta/beta power ratios associated with ADHD.
(Monastra, Monastra et al. 2002)

Neurotherapy v/s Ritalin (4)
- 22 ADHD children received Neurotherapy
- 12 ADHD children received Ritalin
- Both Neurotherapy and Ritalin groups showed improvements on the TOVA, and on the speed and accuracy measures of the Attention Endurance Test.
- Furthermore, ADHD behaviors were significantly reduced in both groups as rated by both teachers and parents on the IOWA-Conners Behavior Rating Scale.
- Findings suggest that Neurotherapy is as effective as Ritalin in improving the behavioural problems of ADHD
(Fuchs, Birbaumer et al. 2003).

Neurotherapy v/s Ritalin (5)
- 31 ADHD children received Neurotherapy. (14 received Neurotherapy training in the clinic 17 at home)
- 31 ADHD children received Ritalin, strated for optimum effect
- Both groups showed clinically significant improvement on TOVA (test of variables of attention) for measures of attention, impulse control, processing speed, and variability in reaction time.
- Both groups had clinically significant improvement and had a large effect size on the Brown ADD Scales.
- The proportion of patients in the Neurotherapy group that significantly improved was equivalent to that in the medication group.
- The Neurotherapy program produced patient outcomes equivalent to those obtained with stimulant drugs.
(Rossiter, 2004)

fMRI study
- Controlled study involving 15 subjects
- Stroop task pre and post 20 sessions of Neurotherapy.
- Behavioural measures
- fMRI Difference between pre and post Neurotherapy
- Found significant changes >+3.0 Std Dev in Right Anterior cingulate and Left Caudate Nucleus

Steady State Visually Evoked Potentials (SSVEP)
- 17 subjects with ADHD, most on Ritalin at intake
- Swinburne University - Brain Sciences Institute

Results
- All subjects permanently off medications (3 yr follow up)
- TOVA normal at 40 sessions (better scores than on Meds)
- Behavioural Measures indicated subjects non-ADHD
- SSVEP indicated > 3.0 Std Dev task related improvements

Duff, 2006 - unpublished PhD study
Neurotherapy and Learning Difficulties

- TOVA, WISC (IQ test) and QEEG were administered to children with Learning Difficulties. They were then divided into two groups with similar socioeconomic status, IQ and TOVA scores.
- One group received Neurotherapy at a rate of 2 half-hour sessions per week for 10 weeks.
- Non-contingent (sham or placebo) reinforcement was given to the control group.
- TOVA, IQ and EEG measures were obtained at the end of the 20 sessions. WISC performance and EEG measures improved only in the Neurotherapy group.
- Results showed improvements in cognitive performance and EEG changes towards normalisation in the Neurotherapy group only (Fernandez, Herrera et al. 2003).

Is there evidence that Neurotherapy normalises brain function? Yes

- Changes in EEG Theta/beta ratio
- Changes in evoked potentials
- Changes in Cerebral Blood flow (fMRI)
- Changes in Steady State Visually Evoked Potentials (SSVEP)
Nine months later (14 year old boy)

- Streptococcus and IBS symptoms normalised (posterior cingulate normalised)
- No anxiety, depression or suicidal ideation.
- IgG food sensitivity transgressions (may be why Alpha still elevated)
- Attention deficit symptoms almost normalised (Foggy head some days)

Summary

- Patients with Autism also can have:
  - Cellular malnutrition
  - Intestinal Dysbiosis (Altered Gut Bacteria ecology)
  - Irritable Bowel Syndrome
  - Leaky Gut
  - Impaired Methylation and Transsulphuration
  - Impaired brain function

- Correction of these underlying pathologies may result in the improvement of associated symptoms.

- Treatment:
  - Biomedical factors
  - ABA Therapy
  - Neurotherapy
  - Speech Therapy
  - Occupational Therapy
  - Sound Therapy

More information?

- http://www.autism.net.au

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