About schizophrenia and psychosis

About one in a hundred people have schizophrenia and can have a variety of 'positive' symptoms, such as hallucinations, delusions or disordered speech/behaviour, and 'negative' symptoms such as problems with fluency of language and thoughts or with expression of emotions.

As is the case with most mental illness, the cause of schizophrenia is not known. The conventional treatment for schizophrenia is usually long-term treatment with antipsychotic medication. A nutritional approach works alongside conventional treatment and may improve both positive and negative symptoms, and also reduce the side-effects of medication.

Below is an outline of nutrition approaches that may be relevant:

- Correcting blood sugar problems made worse by excess stimulant and drug use
- Addressing essential fat imbalances
- Increasing antioxidants; niacin (Vitamin B3) therapy
- Addressing methylation problems helped by B12 and folic acid
- Investigating pyroluria and the need for zinc and identifying any food allergies

Here are a few words from Eddie, he found nutrition key to managing his schizophrenia:

Read on for more information on Schizophrenia/psychosis and how it can be influenced by nutrition. You may also be interested to read this recently published comprehensive review that was run by Food for the Brain, it covers all the evidence regarding nutritional interventions that work with schizophrenia. Also see our nutritional action plan for further advice.

What is Schizophrenia?

Schizophrenia is a progressive psychiatric disorder, which commonly emerges during adolescence and affects almost one in a hundred – over 20 million people across the globe.

Schizophrenia is still a highly stigmatised mental health condition, and there exists a great deal of misinformation and misunderstanding. It is important to remember that schizophrenia does not cause an individual to become violent or dangerous, or to have a split personality (NHS, 2021).

Schizophrenia is a loaded word, feared by patient and public alike. It conjures up images of dangerous and crazy people. In truth, most members of the public have no real idea what is meant by this word, often believing that sufferers have split personalities, like Jekyll and Hyde. About one in a hundred people have schizophrenia and can have a variety of symptoms which are known as 'positive' symptoms and 'negative' symptoms.

'Positive' symptoms include hallucinations, delusions, disorganised speech, disorganised behaviour and inappropriate emotions.

'Negative' symptoms include alogia (problem with fluency of language and thoughts), affective blunting (problems with expression of emotions and feelings), anhedonia (lack of ability to experience pleasure), avolition (lack of ability to start things and follow through), and attentional impairment (lack of ability to focus attention)

A person diagnosed with schizophrenia may have any or all of these, but at a level of severity that makes them either unable to cope or others unable to cope with them.

Most of us have, at some time or other, experienced some level of psychosis, a temporary losing touch with reality as we collectively know it. The normal person recovering from the delusions brought on by a high fever can breathe a great sigh of relief at the thought that his experience was only temporary. The person under the influence of the hallucinogenic drug LSD can at least rely on the clock, since the drug-induced psychosis will wear off with time. Some people's experience of so-called schizophrenia can be likened to a nightmare state from which they may awaken intermittently. For some, schizophrenia is like living in a nonstop nightmare.

Causes of Schizophrenia

As is the case with most mental illness, the cause of schizophrenia is not known. There are a number of theories relating to neurotransmitter imbalances and functional magnetic resonance imaging (fMRI) studies have shown a broad array of brain abnormalities.

The conventional treatment for schizophrenia is usually long-term treatment with antipsychotic medication. While this can be quite effective for the positive symptoms,

there is often little improvement in negative symptoms meaning that the sufferer may have a poor quality of life. On top of that, side-effects of medication can be considerable in some cases, and the newer antipsychotics (known as atypical) can cause rapid and considerable weight gain and increase the risk for diabetes and metabolic syndrome.

A growing body of research has investigated the utility of nutritional approaches as an adjunct to anti-psychotic medication including antioxidant and vitamin B supplementation, neuroprotective and anti-inflammatory nutrients including essential fats, as well as exclusion diets. Whilst none of these interventions provides a 'one-size-fits-all' therapeutic solution, we suggest that a personalised approach warrants research attention as there is growing agreement that schizophrenia is a spectrum disorder that develops from the interplay between environmental, hence nutritional and genetic factors.

The following have also been identified as potential factors:

- Activation in the immune system of the mother prenatally or advanced paternal age at time of conception
- Perinatal hypoxia (as in hypoxic ischaemic encephalopathy) and other pregnancy and perinatal complications
- Use of recreational drugs, such as cannabis, during adolescence
- Lifestyle and environmental factors, such as stress, trauma or living in a polluted city (Schmidt and Mirnic, 2015).

The nutritional approach alongside conventional treatment

A nutritional approach works alongside conventional treatment and may improve both positive and negative symptoms, and also reduce the side-effects of medication. In some cases, the improvements are so great that the patient's doctor may take the decision to cut down or discontinue medication.

At the Brain Bio Centre, the best results we've seen in helping those with schizophrenia or other psychotic disorders are achieved by investigating a number of possible avenues. These include:

- Blood sugar problems made worse by excess stimulant and drug use;
- Essential fat imbalances;
- Too many oxidants and not enough antioxidants;
- Niacin (Vitamin B3) therapy;
- Methylation problems helped by B12 and folic acid;
- Pyroluria and the need for zinc;
- Food allergies.

Quite apart from these nutritional factors, having good psychological support and a stable home environment make a major impact upon those with mental health problems.

Nutritional interventions for the adjunctive treatment of schizophrenia

We funded an MSc, which resulted in an excellent review in 2014 of '**Nutritional interventions for the adjunctive treatment of schizophrenia**' which you can see here https://foodforthebrain.org/?page_id=24095

Some effective treatment strategies:

Some of the effective treatment strategies which we've employed at the Brain Bio Centre, include:

- Correcting high homocysteine levels with supplementation of B6, B12, folate, zinc and TMG.
- Increasing intake of antioxidants, and especially vitamin C and n-acetyl cysteine (NAC).
- High dose niacin eg 1,000mg of 'no blush' niacin. This approach was pioneered by the late Dr Abram Hoffer and well reviewed by his son, Professor John Leonard Hoffer (Hoffer, 2011).
- A low glycemic load diet, devoid of sugar.

- Investigating food intolerances and ruling out coeliacs (gluten sensitivity).

DIET AND NUTRITION: WHAT WORKS?

Balance your blood sugar and avoid stimulants

Your intake of sugar, refined carbohydrates, caffeine, alcohol and cigarettes, as well as stimulant drugs, all affect the ability to keep one's blood sugar level balanced. On top of this common antipsychotic medication may also further disturb blood sugar control. Stimulant drugs, from amphetamines to cocaine, can induce schizophrenia. The incidence of blood sugar problems and diabetes is also much higher in those with schizophrenia.

Therefore it is strongly advisable to reduce, as much as possible, your intake of sugar, refined carbohydrates, caffeine and stimulant drugs and eat a low glycemic load diet.

Increase essential fats

We build our brain from specialised essential fats. Of course, this isn't a static process. We are always building membranes, then breaking them down, and building new ones. The breaking down, or stripping of essential fats from brain, membranes, is done by an enzyme called phospholipase A2 (PLA2). This is often overactive in people with schizophrenia, and this leads to a greater need for these fats, which are quickly lost from the brain. This explains earlier findings that schizophrenic patients have much lower levels of fatty acids in the frontal cortex of the brain. So, what's the evidence that increasing a person's intakes of essential fats makes a difference?

The World Health Organization conducted a survey of the incidence and outcome of schizophrenia in eight countries in Africa, Asia, Europe and the Americas. They found that while the incidence was surprisingly similar in all countries, the outcomes were very different. In some countries, schizophrenia seemed to be a relatively mild and self-limiting disease, whereas in others it was a severe and life-long condition. Of all the factors considered which might explain this, by far the strongest correlation was with the fat content of the diet. Those countries with a high intake of essential fats from fish and vegetables, as opposed to meat, had much less severe outcomes.

Dr Iain Glen from the mental health department of Aberdeen University found that 80 per cent of schizophrenics are essential fat deficient. He gave 50 patients essential fat supplements and reported a dramatic response. A larger placebo-controlled, crossover, 10-month study of the effects of EFA supplementation in schizophrenics, including supplements of zinc, B6, B3 and vitamin C with omega-6 fats, also produced significant improvements in schizophrenic symptoms. Two trials giving omega 3 fish oil high in EPA produced significant improvement. But not all results are positive. A trial using only omega-3 fats versus placebo found no significant improvement in mental health.

Of even greater promise are the results of a study into the preventative benefits of omega-3. This study, published in the British Journal of Psychiatry in 2010, identified 81 young adults aged 13 to 25 years with "ultra-high risk of developing psychosis". They were given (in a randomised, double-blind fashion) 1.2g of omega-3 oil or placebo for a 12 week period and then monitored for a further 40 weeks, so the total study period was 1 year. At the end of the study only 5% of those taking the omega-3, compared with 28% of those taking placebo had developed psychosis. And of the 5% taking the omega-3 who did develop psychosis, they had significantly reduced symptoms (both positive and negative) and improved functioning.

Side effects? Sometimes, when starting omega-3 fish oil supplements, you can experience loose stools or fish-tasting burps. If this happens just try a lower dose.

Contraindications with medication? You shouldn't take high dose omega-3 oils if you are also taking 'blood-thinning' medication.

See our Action Plan for recommendations:

Up antioxidants

There's another part to the essential fat story. These fats are also prone to destruction in the brain, and in the diet, by oxidants. Indeed, there is evidence of more oxidation in the frontal cortex of those with schizophrenia. Therefore, as well as increasing the intake of essential fats, it makes sense to follow a diet (and lifestyle) that minimises oxidants from fried or burnt food and maximises intake of antioxidant nutrients such as vitamins A, C and E. These alone have been shown to help. Vitamin C is also an anti-stress vitamin and may counter too much adrenalin, which is often found in those diagnosed with schizophrenia. Smoking is both a source of oxidants and destroys vitamin C.

Vitamin C deficiency is also far more common than realised in people with mental health problems, often because they don't look after themselves properly and eat poorly.

Professor Derri Shtasel from the department of psychiatry at the University of Pennsylvania, School of Medicine in Philadelphia described a case of a woman who was confused and hearing voices, as well as having physical symptoms. She was tested for vitamin C status and found to be very deficient. After being given vitamin C she had fewer hallucinations, her speech improved and she became more motivated and sociable. Vitamin C has been shown to reduce the symptoms of schizophrenia in research trials, and a number of studies have shown that people diagnosed with mental illness may have much greater requirements for this vitamin – often ten times higher – and are frequently deficient.

Side effects? Excessive vitamin C can cause loose stools in some individuals. If this happens, reduce the dose to a tolerable level.

Contraindications with medication? None known.

See our Action Plan for our recommendations:

Consider niacin

One of the classic vitamin deficiency diseases is pellagra – Niacin (vitamin B3) deficiency. The classic symptoms of this condition are the '3 Ds' – dermatitis, diarrhoea and dementia. A more extensive list of symptoms might include headaches, sleep disturbance, hallucinations, thought disorder, anxiety and depression.

If you have these symptoms you may need a lot more niacin than the basic RDA, sometimes as much as 2,000mg or 100 times the RDA. We call this 'vitamin dependency', but of course we are all vitamin dependent. It's just that some people need more, perhaps for genetic reasons, than others.

The use of 'megadoses' of niacin was first tried by Drs Humphrey Osmond and Abram Hoffer in 1951. So impressed were they with the results in acute schizophrenics that, in 1953, they ran the first double-blind therapeutic trials in the history of psychiatry. Their first two trials showed significant improvement giving at least 3gs (3,000mg) a day, compared to placebos. They also found that chronic schizophrenics, not first-time sufferers but long-term inpatients, showed little improvement. The results of six double blind controlled trials showed that the natural recovery rate was doubled. Later they found that even chronic patients, treated for several years with niacin in combination with other nutrients, often recovered.

Hoffer's discovery was, however, side-lined partly due to some studies which gave niacin to long-term schizophrenic patients who had been on medication for several years and failed to respond to niacin in the short-term.

Since then, Dr Hoffer published ten-year follow-ups on schizophrenics treated with niacin, compared to those not treated with niacin. In the niacin patients there were substantially fewer admissions, days in hospital and suicides. He continued to treat acute schizophrenics with niacin, plus other nutrients, including vitamin C, folic acid and essential fats, and reported a high recovery rate in acute schizophrenics who follow his nutritional programme. Over his long career Dr Hoffer recorded 4,000 cases and published double-blind trials. He was convinced that his approach was a major breakthrough in the treatment of mental illness.

Just how niacin works is still a bit of a mystery. Knowing that people with schizophrenia had hallucinations, Dr Hoffer's explanation was that niacin stops the brain from producing adrenochrome from adrenalin, a chemical known to induce hallucinations. Working together with vitamin B12 and folic acid, niacin helps keep adrenalin and noradrenalin levels in balance, and prevent the abnormal production of adrenochrome in the brain. These nutrients are 'methyl' donors and acceptors, and act intelligently in the brain to keep everything in check. Once again, some people may simply need more to stay healthy.

Niacin, through its flushing action improves oxygen supply to the brain. Niacin is also needed for the brain to make use of essential fats. The 'happy' neurotransmitter serotonin also needs niacin. Serotonin is made from the amino acid tryptophan, but only in the presence of enough niacin. So there are many possible ways this vitamin could affect brain function.

Side effects?

Niacin comes in different forms. Niacin (formerly known as nicotinic acid) causes a harmless blushing sensation, accompanied with an increase in skin temperature and slight itching. This effect can be quite severe, and lasts for up to 30 minutes. However, if 500mg or 1,000mg of niacin are taken twice a day at regular intervals, the blushing stops.

Some supplement companies produce a 'no-flush' niacin by binding niacin with inositol. This works, so it's probably the best form, but it is more expensive. Niacin also comes in the form of niacinamide, which doesn't cause blushing either. It has to be said, however, that both of these forms appear to be slightly less effective than niacin. This may be

because the blushing effect of niacin improves blood flow, and hence nutrient supply to the brain.

Contraindications with medication? None known.

Side effects? The amount of niacin that's needed is around 1 to 6g a day. A minimum therapeutic level is 1g a day. These levels are in the order of 100 times the RDA. Levels of niacin much higher than these, particularly in sustained-release tablets, can be liver toxic. Out of perhaps 100,000 people taking megadoses of niacin at levels of several grams over the past 40 years, there have been two deaths due to liver failure. In a third case, jaundice resulted from a slow-release preparation. When the same patient was placed back on standard niacin, he no longer got jaundice. In any event, anything over 1g is best taken under the supervision of a qualified practitioner. If you become nauseated, that is an indication to stop supplementation and resume three days later, with a lower amount. If you have a history of liver problems, you should have regular monitoring of liver enzymes.

See our Action Plan for our recommendations:

Methylation, B12, folic acid and B6

Methylation is a critical process in the brain that helps maintain the right chemical balance. An indicator of faulty methylation is having a high level of a toxic amino acid in the blood called homocysteine. The body makes homocysteine from dietary protein and, provided you are getting enough of certain vitamins1, especially folic acid, B12 and B6, homocysteine levels decrease. Many people with schizophrenia, especially young males, tend to have a high level of homocysteine, despite no obvious dietary lack of these vitamins. High levels of homocysteine and low blood levels of folic acid have been reported by many research groups. These unusually high levels don't appear to relate to diet or lifestyle factors, such as smoking. People diagnosed with schizophrenia are more likely to have inherited a genetic variation of a key homocysteine lowering enzyme, which may make them need more of these and other nutrients.

Research at Kings College Hospital psychiatry department in London has found high doses of folic acid to be highly effective in schizophrenic patients. They used 15mg a day, which is 75 times the RDA! Folic acid is not toxic at this level. We recommend starting with 1mg a day, increasing the dose only under supervision of your health care provider.

Vitamin B12, which like folic acid is involved in methylation, has also been shown to help schizophrenic patients. Vitamin B12 is difficult to absorb, especially in large amounts,

and some doctors have reported good results giving weekly, or twice-weekly, injections of 1mg of vitamin B12. A form of B12, methyl B12, is more easily absorbed, and B12 can be taken in sub-lingual form which is even better absorbed.

Supplementing a combination of folic acid, B12, B6, along with a methyl donor called TMG, the mineral zinc and the antioxidant N-Acetyl-Cysteine has been shown to most effective in improving mental health, and lowering the homocysteine levels of schizophrenia patients with high homocysteine levels.

Side effects? Folic acid supplementation can mask the symptoms of an underlying B12 deficiency, so we don't recommend supplementing folic acid on its own.

Contraindications with medication?

See our Action plan for our recommendations:

Are you pyroluric? The zinc link

Possibly one of the most significant 'undiscovered' discoveries in the nutritional treatment of mental illness is that many mentally ill people are deficient in vitamin B6 and zinc. But this deficiency is no ordinary deficiency: you can't correct it by simply eating more foods that are rich in zinc and B6. It is connected with the abnormal production of a group of chemicals called 'pyrroles'. A person with a high level of pyrroles in the urine needs more B6 and zinc than usual, since they rob the body of these essential nutrients, increasing a person's requirements to stay healthy. At the Brain Bio Centre, we find many people diagnosed with schizophrenia have 'pyroluria'.

The test for pyroluria is remarkably simple and very inexpensive. When you add a chemical known as Erhlich's reagant to urine, it will turn mauve if there are krytpopyrroles present. Dubbed 'mauve factor' in the 1960s, this was found in 11 per cent of normal people, 24 per cent of disturbed children, 42 per cent of psychiatric patients and 52 per cent of schizophrenics. Dr Carl Pfeiffer and Dr Arthur Sohler at Princeton's Brain Bio Center worked out that these abnormal chemicals would bind to B6 and zinc, inducing deficiency. With this knowledge, effective therapy was at hand.

The Signs and Symptoms of Pyroluria
Pyroluria is often a stress-related condition, with symptoms usually beginning in the teenage years after a stressful event such as exams or the breakup of a relationship.

Pyrolurics often have weak immune systems and may suffer from frequent ear infections as a child, colds, fevers and chills. Other symptoms include fatigue, nervous exhaustion, insomnia, poor memory, hyperactivity, seizures, poor learning ability, confusion, an inability to think clearly, depression and mood swings. In girls there can be irregular periods and in boys relative impotence. The pyroluric patient can have bad breath and a strange body odour, a poor tolerance of alcohol or drugs, may wake up with nausea, and have cold hands and feet and abdominal pain.

A lack of dream recall is very common. It is normal to remember dreams, and many people, whether or not they have mental health problems, report better dream recall once they start supplementing optimal amounts of vitamin B6 and zinc. Other tell-tale signs include pale skin, white marks on the nails and, in extreme cases, poor hair growth and loss of hair colour. Often a person with pyroluria also has skin problems such as acne or eczema.

Not all these symptoms are present in all pyrolurics, but if you are experiencing a number of them, it is well worth testing for.

Side effects? No single nutrient should be supplemented at high levels over the long-term without retesting the need to do so as imbalances can occur. Vitamin B6 can be toxic at high doses, the key symptom of which is tingling hands or fingers. If this occurs, stop the B6 immediately and the tingling will stop within 1-3 days. Once it has stopped, you could restart the B6 at half the previous dose.

Contraindications with medication? None known

Check for allergy

Some people with mental health problems are sensitive to gluten, especially wheat gluten, which can bring on all sorts of symptoms of mental illness. This has been known since the 1950s, when Dr Lauretta Bender noted that schizophrenic children frequently had coeliac disease (severe gluten allergy). By 1966 she had recorded 20 such cases from among around 2,000 schizophrenic children. In 1961 Drs Graff and Handford published data showing that four out of 37 adult male schizophrenics admitted to the University of Pennsylvania Hospital in Philadelphia had a history of coeliac disease in childhood.

These early observations greatly interested Dr Curtis Dohan at the University of Pennsylvania. He suspected that the two were linked and decided to test his theory by randomly placed all men admitted to a locked psychiatric ward in a Veterans

Administration Hospital in Coatsville, Pennsylvania, either on a diet containing no milk or cereals, or on one that was relatively high in cereals. (Milk was eliminated from the diet because some people do not benefit when only glutens are removed.) All other treatment continued as normal. Midway through the experiment, 62 per cent of the group on no milk and cereals were released to a 'full privileges' ward. Only 36 per cent of those patients receiving a diet including cereal were able to leave the locked ward. When the wheat gluten was secretly placed back into the diet, the improved patients once again relapsed.

These results have since been confirmed by other double-blind placebo-controlled trials. In one, published in the Journal of Biological Psychiatry, 30 patients suffering from anxiety, depression, confusion or difficulty in concentration were tested, using a placebo-controlled trial, as to whether individual food allergies could really produce mental symptoms in these individuals. The results showed that allergies alone, not placebos, were able to produce the following symptoms: severe depression, nervousness, feeling of anger without a particular object, loss of motivation and severe mental blankness. The foods/chemicals that produced most severe mental reactions were wheat, milk, cane sugar, tobacco smoke and eggs.

However, more recent research hasn't found that coeliacs disease in more prevalent among those with schizophrenia or vice versa. However, the possibility of allergy to other foods may be worth investigating, especially if allergic symptoms, including eczema, asthma, digestive problems, ear infections, sinusitis or rhinitis are also present. At the Brain Bio Centre we frequently find that food intolerances to a range of foods appear to be contributing to symptoms, so investigating all types of food sensitivities is recommended.

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Body Systems identified as playing a role in presentation of the disease

Moreover, disruptions in various body systems have been identified as playing a role in the presentation of the disease. Elucidated below are several pathophysiological mechanisms and biological systems which have been implicated in the pathogenesis of schizophrenia.

Disruptions of Telomere Biology

Individuals with schizophrenia have been demonstrated to have shorter telomere length, a marker of biological aging. One potential explanatory mechanism for this is that individuals with schizophrenia may have genetic variants for the TERT (telomerase reverse transcriptase) gene, which encodes telomerase, the enzyme responsible for maintaining telomere length integrity (Rao et al., 2016). Further proposed mechanisms for shortened telomere length in schizophrenia are via processes of inflammation, chronic stress and oxidative stress (Corfidir et al., 2021).

Microbiota Gut-Brain-Axis Disruption

Tight Junction Modulators

Zonulin associated with tight junction permeability for endothelial cells, in the intestinal barrier, and claudin-5 and -12, associated with tight junction permeability in the blood brain barrier,, (BBB), have both been implicated in schizophrenia (Greene, Hanley and Campbell, 2019; Fasano, 2012). Zonulin levels may rise in response to heavy alcohol consumption (Patel et al., 2015), smoking (Malickova et al., 2017), as well as exposure

to gluten, indicating increased intestinal permeability (Fasano, 2012). Claudin-5 levels have been observed to decrease following exposure to high levels of glucose, and the heavy metal, lead (Pb), resulting in increased permeability of the BBB (Jia et al., 2013). Furthermore, the aforementioned TERT gene has extra-telomeric functions, and impairment of the gene as a result of oxidative stress, a hallmark of schizophrenia, results in the downregulation of proteasome 26S activity (Im et al., 2017). Impaired activity of proteasome 26S reduces degradation of occludins and zonulin, which in turn decreases transepithelial resistance and contributes to intestinal and BBB permeability (Andersen et al., 2010; Im et al., 2017).

Microbiota Composition

Imbalances in the gut microbiota and subsequent dysfunction via the gut-brain axis has been suggested to be a key consideration for schizophrenia. This may result in increased neuronal and synaptic damage, as a result of increased inflammation and neurotoxin synthesis (Yuan et al., 2019). Dominance of particular strains of gut bacteria have also been observed to be associated with disease onset of schizophrenia and related symptoms. Age of onset of the disease has been associated with dominance of *Cyanobacteria* in the gut microbiota, and increased levels of *Lactobacillus phage phiadh* have also been observed in patients with schizophrenia (Kraeuter, 2020).

The following strains have been identified as being dominant in the gut microbiome of individuals with schizophrenia:

- *Succinivibrio*
- *Megasphaera*
- *Collinsella*
- *Clostridium*
- *Klebsiella*
- *Methanobrevibacter (Shen et al., 2018).*

However, levels of the following observed to be reduced in the gut microbiome of individuals with schizophrenia:

- *Blautia*
- *Coprococcus*
- *Roseburia (Shen et al., 2018)*

Disrupted Neurotransmitter Synthesis and Functioning

Until recently, research has focused primarily on a dopamine hypothesis, which proposes that aberrant functioning of this neurotransmitter plays a key role in the pathophysiology of schizophrenia. However, presently research has expanded to propose an integrated theory of complex interplay, involving disrupted functioning of the dopaminergic, glutamatergic, serotonergic, and gamma-aminobutyric acid (GABA) signaling systems (Yang and Tsai, 2017).

Serotonin

Dysfunctional activation and function of serotonin has been suggested to play a role in the pathology of schizophrenia. Serotonin is involved in the brain in social behaviour, mood and sensory modulation, executive functioning, communication between brain cells, and is also vital for sleep, appetite regulation and digestion. Reduced availability of serotonin has been suggested to result in increased incidence of cognitive fragmentation, which impacts on the brain's ability to filter out irrelevant information and manage sensory overload (Patrick and Ames, 2015).

Insufficiency of serotonin has also been linked to increased aggression and self injurious behaviour. The serotonin-derived metabolite, 5-hydroxy-indole acetic acid (5- HIAA), as derived from the cerebrospinal fluid, is considered a biomarker for reduced serotonin levels in the brain. Another consideration for individuals with schizophrenia may be genetic variants on the gene TPH2, along with other serotonin modulating genes. Some genetic variations of this gene may affect the biosynthesis of serotonin. And therefore contribute to the pathophysiology of the disease via mechanisms of defective and insufficient serotonin synthesis (Patrick and Ames, 2015).

Dopamine

Dopamine hyperactivation has also been implicated in the pathogenesis of schizophrenia (Kraeuter, 2020). Increased synthesis of dopamine, particularly in response to stress, has been observed in individuals with the disease, and this has been correlated with altered cortical and cognitive functioning. Furthermore, (Howes et al., 2017). Altered hippocampal activity, as observed in schizophrenia, is also thought to be correlated with increased levels of dopamine (Kraeuter, 2020).

Glutamate

Impaired glutamate neurotransmission has also been hypothesised to be involved in schizophrenia pathology (Kraeuter, 2020), particularly via N-methyl-d-aspartate receptor (NMDAR) functioning due to disrupted circuitry in the brain (Uno and Coyle, 2019).

GABA

RELN, NRG1/ErbB4, and BDNF are all involved in the establishment of circulatory GABA signalling. It has been theorised that alterations to these processes during gestational brain development may be involved in the aetiology of schizophrenia, due to impaired GABA signalling (Egerton et al., 2017). GABA levels have also been observed to be lower in individuals with schizophrenia compared with individuals without the disease ($p = 0.02$) (Kumar, Vajawat and Rao, 2021).

Impaired Glucose Metabolism

Impaired glucose metabolism and insulin resistance has been implicated in schizophrenia, as imbalanced glucose levels have been observed in the cerebrospinal fluid of patients diagnosed with the disease (Roosterman and Cottrell, 2021). Additionally, schizophrenia has been associated with an increased risk of type II diabetes development, glucose intolerance, and elevated fasting blood glucose and insulin levels have been observed clinically in presentations of the disease (Pillinger et al., 2017). Hyperglycaemia causes cortisol synthesis to be increased, which impacts on the regulation of adipose tissue accumulation and storage and may also affect appetite control and energy intake balance, as these functions are glucocorticoid-regulated bodily functions (Epel et al., 2001).

One potential mechanism for the involvement of impaired glucose metabolism in schizophrenia pathology is via disruption of mTOR mitochondrial pathway (Bryll et al., 2020). Consumption of sugar and processed foods leads to hyperglycaemia, which impairs pancreatic beta cells' ability to regulate blood glucose and insulin. Hyperglycaemia induced oxidative stress activates the JNK pathway, which initiates apoptosis of pancreatic beta cells, causing insulin insufficiency and impaired glucose tolerance (Bachar et al., 2009). Hyperglycaemia also stimulates mTORC1 and induces oxidative stress in mitochondria. Disruption of the mTOR pathway increases β- and γ-secretases, which alter APP metabolism (Cai et al., 2015). Activation of the mTOR and JNK pathways also impairs hTERT, which may increase degeneration in the brain (Cai et al., 2015). This is because hTERT has been hypothesised to be neuroprotective, because it localises within mitochondria and protects neurons from oxidative stress, DNA damage and neuronal apoptosis (Miwa and Saretzki, 2016).

Nutrition and Schizophrenia

Nutritional psychiatry is an emerging field of research, which investigates the role of nutrients in brain health and their salience and potential application to psychiatric

disorders (Sarris et al., 2015).

The following factors have been identified as pertinent nutritional interventions to address in Schizophrenia.

Ketogenic diet

A ketogenic diet, which is lower in carbohydrates and higher in protein / fats, may improve clinical presentations of schizophrenia through reducing metabolic symptoms. Furthermore, in animal models of schizophrenia, a ketogenic diet has been observed to significantly ameliorate the disease. However, further research is required to explore this in human models (Sarnyai, Kraeuter, Palmer , 2019). Further evidence has suggested that ketogenic diets may be beneficial in schizophrenia, due to exerting positive effects of hypometabolism, neurotransmitter imbalances, oxidative stress and inflammation (Norwitz, Dalai, Palmer, 2020). Glucose levels were observed to be reduced as a result of a ketogenic diet, and therefore this diet may be useful for improving symptoms of impaired glucose metabolism in the disease. Moreover, cognitive and memory disturbances have been observed to be improved following implementation of a ketogenic diet (Bostock, Kirby and Taylor, 2017). Adopting a ketogenic diet may also be useful for increasing tryptophan, which may in turn help to increase levels of serotonin.

Tryptophan

Depletion of the essential amino acid, tryptophan, is a highly merited consideration for schizophrenia, due to the role of tryptophan in the synthesis of serotonin. Impact of tryptophan deficiency, and subsequent serotonin insufficiency, can be observed via adverse effects on the prefrontal cortex of the brain, in terms of reduced impulse control and impaired decision making. Furthermore, tryptophan insufficiency has been associated with overactivation of the ventral striatum, which is a part of the brain involved in short term decision making, and underactivation of the dorsal striatum, which is involved in long term decision making. However, supplementation of tryptophan has been observed to rectify this imbalance (Patrick and Ames, 2015).

Gut Health

Prebiotics

Prebiotics may increase the expression of gut hormones such as peptide tyrosine tyrosine, glucagon-like peptide 1 and leptin, which may increase satiety, whilst decreasing levels of hunger hormones, such as ghrelin (Kao, Burnet and Lennox, 2018).

Prebiotics may therefore be useful for addressing metabolic symptoms in schizophrenia, such as impaired glucose metabolism.

Cruciferous and sulphurous vegetables, such as broccoli, leeks, onions and garlic, are sources of prebiotic fibres, such as inulin (Swennen, Courtin and Delcour, 2006).

Inulin specifically has been shown to reduce circulating levels of Zonulin, which may help to support intestinal barrier integrity, reduce levels of ghrelin and increase the production of short chain fatty acids (SCFAs), such as butyrate, propionate and acetate (Swennin, Courtin and Delcour, 2006). SCFAs are integral for the balance of gut microbiota. Butyrate may help to regulate glucose and energy homeostasis and help prevent gut dysbiosis through beta-oxidation (De Vadder et al., 2014; Byndloss et al., 2016). Propionate is transported to the liver, where it has been observed to be involved in the regulation of gluconeogenesis and satiety signalling, as it interacts with fatty acid receptors in the gut (De Vadder et al., 2014). Acetate is transferred to peripheral tissues, where it is involved in cholesterol metabolism, lipogenesis and regulation of appetite (Frost et al., 2014).

Probiotics

Gut microbiota are essential for the synthesis of neurotransmitters. *Lactobacillus* and *Bifidobacteria* are involved in the production of Gamma aminobutyrate (GABA), and Bacillus spp is important for the synthesis of dopamine. *Candida albicans, Escherichia, Streptococci*, and *Enterococci spp* are all involved in the synthesis of serotonin (Grover et al., 2019).

Consuming fermented foods such as kimchi, sauerkraut and kefir and taking a broad spectrum probiotic may be beneficial for increasing the strains of different bacteria in the gut microbiota.

Gluten Elimination Diet

Research looking at a sample of participants who had schizophrenia or had not been diagnosed with the disorder, observed that there was a higher incidence of gluten intolerance in individuals diagnosed with schizophrenia, compared with those without the diagnosis (Jackson et al., 2014). Therefore asking one's physician for a coeliac test is important, to rule out coeliac's disease. However, it should be noted if the test is negative, an individual may still be non coeliac gluten sensitive and therefore adopting a gluten free diet may be beneficial.

Omega 3

Omega-3 supplementation may impact on dopamine and glutamate transmission, oxidative stress, inflammation, myelination, and neurotransmission pathways. Omega-3 has been linked to improved symptoms in those experiencing a schizophrenic episode (Frajerman et al., 2021). Moreover, A randomized placebo-controlled trial was conducted over 26 weeks to study whether omega-3 fatty acids would have an effect on symptom severity in first episode schizophrenic patients. 71 patients were assigned either a placebo of olive oil or 2.2g/day of omega-3 supplement. Severity of symptoms were measured using the positive and negative syndrome scale (PANNSS). A 50% improvement in symptom severity was recorded more frequently in the omega-3 group compared to the placebo group. Significant improvements were found in depressive symptoms, the level of functioning and clinical global impression when patients were supplemented.

These findings suggest that a 6-month intervention of omega-3 supplementation may be able to decrease symptom severity in first episode schizophrenia patients (Pawełczyk et al., 2016).

Vitamins and Minerals

B Vitamins

Folate, Vitamin B6 and Vitamin B12 have all been suggested to be key considerations for schizophrenia, due to their essential function in methylation and the lower serum levels commonly observed clinically in patients with schizophrenia (Wang et al. 2016). Methylation is a vital biochemical process used by the body to module the expression of genes. When there is a deficiency of folate, B6 and B12, homocysteine levels can build up, as these vitamins metabolise homocysteine into cysteine. When homocysteine levels accumulate, this can cause an excessive build up, or hyperhomocysteinaemia, to occur. Hyperhomocysteinaemia impairs the integrity of the blood-brain-barrier (BBB) and causes neurodegeneration, and has been implicated in the pathophysiology of schizophrenia (Kalani et al., 2014; Teasdale et al., 2020).

Vitamin D

Study was conducted to understand whether vitamin D supplementation, especially sunlight exposure, would have an impact on negative symptoms of those with schizophrenia. 52 patients took part in the study and had their serum 25 OH Vitamin D

levels were then measured to understand their current vitamin D level in the blood. The severity of symptoms was measured using the scale for the assessment of negative symptoms (SANS). The mean SANS score was statistically significantly lower after replacement of vitamin D, the total attention score was also significantly improved. The study concluded that addressing vitamin D deficiency in schizophrenic patients can improve symptoms of schizophrenia (Neriman et al., 2021).

Iron

A study was conducted to identify whether low blood iron levels could be related to severity of schizophrenia symptoms. This study was conducted on 121 patients during their first episode of schizophrenia disorder. Symptoms were measured using the positive and negative syndrome scale (PANSS), and iron deficiency was defined as a serum ferritin less than 20ng/ml. The study found patients with iron deficiency were significantly more likely to have more prominent negative symptoms, and patients with more negative symptoms had significantly lower serum ferritin (iron) levels than their counterparts. This study highlights a possibility for further investigation as to whether iron supplementation could be used as an intervention (Kim et al., 2018).

Note: Any nutritional interventions should be implemented only under the supervision of a GP and psychiatrist and with the support of a qualified nutritional professional.

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