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Schizophrenia is a stress memory whose prominent symptom is psychosis: a literary update

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ABSTRACT

Two distinct schools of thought and two men have continued to dominate psychiatry over the past century. Despite both of these men supporting eugenics; Emil Kraepelin and Paul Eugen Bleuler also held very different views on how better outcomes could best be achieved. Progress in the delivery of better outcomes for schizophrenia has halted. Gaining an understanding of the neurobiology involved in schizophrenia may facilitate the delivery of better clinical outcomes. An extensive narrative review of the literature was undertaken to ascertain a neurobiological basis for schizophrenia. This review revealed a metabolic disorder that produces an adaptation to chronic nutrient or hypoxic stress. The formation of a stress memory will be explored. An evidence base will be presented to support rationale for relabeling psychiatric disorders as a stress memory with prominent symptoms. For instance, psychosis, mood disturbance, persistently low mood, anxiety or a delayed reaction in the case of post-traumatic stress disorder. Besides the argument for neurobiological and symptom accuracy, an appropriate name change may be prudent to reduce the burden of stigma that was derived from the eugenics movement and which continues to defame people today.

Keywords: schizophrenia, post-traumatic stress disorder, bipolar disorder, depression, anxiety

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INTRODUCTION

Serendipitous treatments for mental illness have been developed that have paved the way for community discharge. However, there has been little real progress in the field of psychiatry for close to a century. Two distinct schools of thought and two men have continued to dominate psychiatry. On one hand, the German psychiatrist, Emil Kraepelin (1856-1926) and on the other was a Swiss psychiatrist, Paul Eugen Bleuler (1857-1939). The two men had very different views on the nature and cause of dementia praecox or schizophrenia.

The French term, demence precoce was coined in 1381 to describe mental deterioration (Aderibigbe et al, 1999). The term dementia praecox is often incorrectly attributed to Emil Kraepelin. However, he was known for his dichotomy which differentiated dementia praecox from manic-depression (Kraepelin, 1987). Emil Kraepelin analysed medical records to emphasise aetiology and outcome in his work; believing that dementia praecox had a biological and genetic origin. He believed improvements in the condition would be temporary and that relapse was the likely progression (Aderibigbe et al, 1999). Kraepelin observed links between myxoedema (a skin condition associated with hypothyroidism) and psychosis (Sjmpson et al, 1963). He thought that dementia praecox would be found to be a metabolic disorder affecting the whole body and tested this assumption by the oral administration of desiccated thyroid glands with limited success (Noll, 2007). Desiccated thyroid glands were the fore runner to thyroid hormones, which were not isolated until much later.

Eugen Bleuler also noticed links between hypothyroidism and schizophrenia (Sjmpson, 1963). He verified the clinical presentations that were described by Emil Kraepelin, however his interpretation of the information conflicted with Kreapelin's view (Kuhn, 2004). Eugen Bleuler based his assumptions on clinical case studies and utilised practical demonstrations as props for his lectures such as, the induction of epileptic seizure by an injection of cardiazol (Kuhn, 2004). By 1908, Eugen Bleuler had refuted dementia praecox and instead coined his own term, schizophrenia (Kuhn, 2004). The literary meaning of the term, split-mind was chosen to represent a dynamic structure in contrast to the static nature of the term, dementia (Kuhn, 2004). His criticism of dementia praecox was that it did not necessarily present in adolescence and its course was not always deteriorative (Aderibigbe et al, 1999). Eugen Bleuler was particularly interested in the notion of the unconscious mind. He was heavily influenced by the work of Sigmund Freud and his pupil, Carl Jung (psychological aspect) (Aderibigbe et al, 1999). Bleuler used the term schizophrenia to describe the separation of the mind from reality.

Both men were advocates of the eugenics movement. The eugenics movement was seen as a means of improving the human race through advocating for desirable traits. Eugenics is a term that was coined by Sir Francis Galton, a psychologist and half cousin of Charles Darwin. Charles Darwin published a landmark book which was entitled, 'The Origin of Species by means of natural selection; or, the preservation of favoured races in the struggle for life' (Darwin, 1872). This work outlines natural selection across all species by adaptation to their environment. In his work, Charles Darwin describes observable gene expression that can be passed to offspring if it persists (O'Brien et al, 2002). His hereditary mechanism was a pangenesis theory. Sir Francis Galton recovered from an anxiety disorder following the death of his father, sufficiently to link Charles Darwin's theory of natural selection to hereditary genetics (Brave, 2014). Sir Galton did so by proving that blood was not the hereditary vector. His view altered the course of psychiatry. Darwin argued that Sir Galton had misinterpreted his work. However, the notion of pangenesis was discredited and Mendelian genetics was instead embraced by the scientific community, as the cause of schizophrenia.

It was a group of German psychiatrists (led by Alfred Ploetz and his brother-in-law Ernst Rudin), who augmented the racial aspect of eugenics. Ernst Rudin was a one-time pupil of Emil Kraepelin and laboratory assistant to Eugen Bleuler. He presented his work as evidence for political action involving 'racial hygiene'. The 'empirical prognoses' of mental illness, was suggested by Rudin as a recessive gene. Hundreds of thousands of mentally ill people across Europe were murdered at the hands of psychiatry. The psychiatrists aimed to remove the recessive gene that carried schizophrenia and continued to act independent of the Nazi party, even after Hitler withdrew his support for their work (Breggin, 1993). Emil Kraepelin argued against a recessive gene based on evidence from sibling studies (Gottesman & Sheilds, 1982). Not to be put off by the truth, Ernst Rudin offered a double recessive gene hypothesis instead. Following the attempts across Europe to wipe out the 'recessive gene that was thought to cause schizophrenia', the disorder reappeared rapidly. This current work is dedicated to the people who lost their lives at the hands of psychiatry. Today it is widely accepted that genetics merely represents vulnerability for developing schizophrenia.

So what is the answer? With the vast number of papers being dedicated to the subject, it would be of interest to establish if schizophrenia is a metabolic disorder. This question is of interest clinically, for developing better health outcomes and for educating the public about the disorder. The aim of this review is therefore to establish a neurobiological explanation for schizophrenia.

MATERIALS AND METHOD

An extensive narrative review of the literature was undertaken to ascertain the relevant neurobiology associated with schizophrenia. The subheadings used to describe the findings are based around themes. These themes aim to clarify the often complex neurobiology for the reader. Topics covered neurochemistry, brain imaging, genetics, neurodevelopmental studies, apoptosis and viability, epigenetic factors, the antioxidant defence system, metabolic processes in the brain and signalling pathways. The review was hampered by articles that may have been written as an attempt to find biomarkers or pharmaceutical targets. These papers only examined portions of biochemical signalling pathways. This review did not focus on psychological or social theories. The review also excluded repetitious articles, where the evidence was not strong and papers which compared various pharmaceutical or nutraceutical treatments. Engines such as, Google scholar, CINAHL, Psych INFO, Medline, Pubmed and Embase were searched between 2008 and 2017. An estimated 16,000 papers were assessed over this period.

RESULTS AND DISCUSSION

Risk factors associated with lifestyle

Firstly, I will pick up from the work of Kraepelin and Bleuler. Emil Kraepelin documented nutrient stress in the form of fluctuating eating patterns (from refusal to eat to ferocious binges) amongst people diagnosed with schizophrenia (Strassnig et al, 2005). Since then, several studies have linked the rise of schizophrenia to the aftermath of periods of caloric restriction that have occurred throughout history such as, the Chinese famine of the 1950s and the earlier Dutch hunger winter (Florean, 2014). William Shakespeare's character Edgar as Tom, in his play King Lear, exhibited psychotic symptoms and layered clothing. His play was first performed around 1606. At this time England was in the grips of an outbreak of the bubonic plague which followed a famine in 1586.

Prior to the use of modern pharmaceuticals to treat mental illness; data pertaining to the New Zealand environment, public health and population diet was collected by Sir Charles Hercus and his team. This historical data was compared to the documents obtained from New Zealand's mental hospitals for the same year (Laupu, 2016). The reanalysis reveals micronutrient deficiencies. Iodine, selenium and iron, which are needed for thyroid hormone production and brain health, were undersupplied to a portion of the New Zealand population at this time (Laupu, 2016). Iron is essential to the brain for cognitive abilities such as, attention span, intelligence, sensory perception, emotions and behaviour (Ignacio, 2014). During fasting states, iodine depletion is observed to occur rapidly (Hercus et al, 1931). Dietary deficiencies of selenium and iron are thought to enhance this iodine deficiency to impair thyroid hormone production (Triggiani et al, 2009). Thyroid hormones directly

interact with the master regulators of both metabolic and redox processes, to mediate the effects of caloric restriction (Sykiotis et al, 2011). Sir Charles observed that the presence of infection increased metabolic demand (Hercus et al, 1925) to explain links between schizophrenia and viral infections (Yolken & Torrey, 1995).

Contributors to the source of caloric restriction may differ today as our food does not tend to be sourced locally anymore. However, micronutrient deficiencies remain a modern concern. For instance, poor nutrition is documented amongst 74% of illicit substance addicts (Islam et al, 2002). The regular use of illicit substances, smoking tobacco products or the heavy intake of alcohol is commonly found, amongst schizophrenia populations today, to increase oxidative stress (Hritcu et al, 2009; Ignatowicz et al, 2013; Cunha-Oliveira et al, 2013). These lifestyle factors are thought to have a pervasive and negative influence by exacerbating the symptoms of schizophrenia. A medical history of traumatic brain injury is a potential risk factor, although this risk associated with a mild hypoxia has not been quantified. There has also been a considerable amount of work invested in exploring neurodevelopmental factors in schizophrenia. Findings from this approach remain inconclusive. Small variations between seasons of birth in schizophrenia are reported and linked to nutrient intake amongst pregnant women (Watson et al, 2007).

Lifestyle factors associated with psychosis certainly point towards caloric restrictions and poor eating patterns that produce nutrient stress. The brain is an organ requiring adequate oxygen and specific nutrients to fuel the work of cognitive functioning. Our brain has an ancient mechanism to cope with seasonal variation in nutrient intake. Metabolic processes allow for these seasonal variations in nutrient intake, however brain energy requirements are tightly regulated (Csete & Doyle, 2004). An inability to meet the brain's energy requirements is involved in schizophrenia. This is evidenced by mitochondrial pathology on post mortem, which indicates a lessened capability to respond to the brain's energy requirements (Kung & Roberts, 1999).

Prodromal period

There is a conspicuous lack of literature exploring neurobiology in the prodromal phase of schizophrenia. Emil Kraepelin linked psychosis to myxoedema, which is known to be latently expressed (Easson, 1966). Myxoedema is a thyroid condition. The thyroid gland, located at the front of the windpipe, regulates metabolism. Enlargement of the thyroid gland is known as goitre. Eugen Bleuler recorded the presence of large goitres in schizophrenia (Sjmpson et al, 1963). This finding was later verified by Sir Charles Hercus during goitre examinations at a Christchurch mental hospital (Hercus & Aitken, 1933).

The prodromal period in schizophrenia is assumed to be a latent expression; perhaps as a consequence of failed integrative stress responses once a threshold is reached (Kroemer et al, 2010). The integrative response to stress amalgamates the regulation of nutrient intake, intermediary metabolism, cell fate and autophagy to protect cellular survival in the brain (Kroemer et al, 2010). This machinery launches the response to nutrient stress that changes gene expression.

First episode of psychosis

Nutrient expenditure and storage is regulated by thyroid hormones to protect energy stores in the brain during periods of nutrient stress (Mullur et al, 2014). When cellular energy and nutrient levels are low, then signals are activated that conserve energy reserves for essential brain functions. This occurs in the presence of selenium deficiency (He et al, 2016). So intracellular signalling pathways that have a heavy demand for energy are suppressed, while simultaneously signalling pathways which do not require much energy are enhanced (Tao et al, 2010). The cell therefore responds to stress by either signalling for cell viability or cell death (apoptosis). These cellular responses to stress are influenced in the brain, by metabolic and redox processes (Foyer, 2005) that provide viability signals for the neuron to survive (Kitagishi et al, 2012; Wrutniak-Cabello et al, 2001).

Changes to high energy demanding brain functions such as, energy and phospholipid metabolism are associated with the expression of cognitive deficits in schizophrenia (Khaitovich et al, 2008). Thyroid hormone activity also adjusts intermediary metabolism involving proteins (Muller & Seitz, 1984). So that disruptions to thyroid hormone availability affect the mobilization and degradation of lipids, to increase the risk of cardiac events arising from dyslipidaemia (Pucci et al, 2000). This finding may clarify a correlation between the presence of schizophrenia and a higher incidence of metabolic syndrome.

During periods of nutrient and energy flux, activation of the transcription factor, Nrf2 enable brain cells to adapt to stress (Hayes & Dinkova-Kostova, 2009). Disrupted thyroid hormones directly activate this transcription factor (Romanque et al, 2011) to explain the suboptimal activation of Nrf2 in schizophrenia (Genc & Genc, 2009). In turn, Nrf2 activation also regulates perturbed antioxidant response and lipogenic gene expression (Huang et al, 2010) which is another key feature of schizophrenia neuropathology. With Nrf2 unable to direct metabolic responses, redox processes are required to maintain cellular homeostasis. Impeded redox coupling may enable heavy metals to accumulate. Serum and hair samples contain variable levels of heavy metals across mental illnesses (Rahman et al, 2009; Karim et al, 2006). Increased levels of the heavy metals lead, cadmium and chromium are documented in schizophrenia (Arinola et al, 2010). Impairments to redox coupling mechanisms suppress cell

viability signals (Gao et al, 2014) and influence mitochondria (Yao et al, 2006) enabling oxidative stress to accumulate, damaging proteins, lipids and DNA in schizophrenia. By the first episode of psychosis there is substantial evidence that the brain's antioxidant enzymes are already in disarray and oxidative stress is present (Sarandol et al, 2015). The presence of oxidative stress indicates the brain's cells are in an unhealthy state and are not coping with reactive oxygen or nitrogen species. A likely explanation is that, in addition to selenium, iron, zinc and iodine; the brain requires the micronutrients copper, manganese and magnesium (Bourne, 2006). These micronutrients also form components of antioxidant enzyme (Vural et al, 2010) and transport proteins used by metabolic pathways (Tapiero & Tew, 2003).

The role of the antioxidant defence system is to protect the brain from environmental insult. Low levels of glutathione S-transferase and metabolising gene polymorphisms are implicated in the development of environmental sensitivities (Schnakenberg et al, 2007). These environmental sensitivities are relevant to perceptual disturbances and lead to paranoid thoughts in schizophrenia.

Symptom expression

Hypoxic-driven gene expression reduces thyroid hormone signals (Simonides et al, 2008). These disrupted thyroid hormone signals interfere with metabolic reprogramming of brain cells following hypoxic episodes (Hochachka et al, 1996) to explain schizophrenia and hypoxic linkages. Neurons in the central nervous system are not very capable of regeneration and instead rely on this reprogramming, known as autophagy. The autophagy process recycles cellular materials and degrades infectious particles (Laplante & Sabatini, 2012). Insufficient autophagy prevents the neurons from reprogramming to signal for cell viability. These alterations are also linked to the gene expression of glutamate transporters in schizophrenia (Smith et al, 2001).

Thyroid hormone signals are responsible for energy metabolism (McAninch & Bianco, 2014). Autophagy is dependent on the energy metabolism pathway, which also controls impaired membrane trafficking and apoptosis in schizophrenia. Incorporated into this energy metabolism pathway is the beclin 1 network. There is post mortem evidence that beclin1 levels are 40% lower in schizophrenia (Merenlender-Wagner et al, 2015). This impaired beclin 1 network alters microstructures in the thalamus (Agarwai et al, 2008) to negatively influence the regulation of the sleep/wake cycle and relay of sensory and motor signals (with the exception of olfactory signals). This activity is relevant to disturbances in spatial memory and executive functioning.

Epigenetic factors

The task of adjusting beclin 1, for neuron viability, is regulated by microRNA (Kang et al, 2011). Hence, microRNA are the master regulators for the silencing of epigenetic gene expression, relevant to schizophrenia, bipolar disorder, anxiety and depression (Hommers er al, 2015). Disrupted thyroid hormone receptor binding is capable of influencing gene expression, RNA processes and protein synthesis to alter cellular functions. Thyroid hormones regulate 5% of genes at a transcriptional level that are required for mood, behaviour, circadian rhythms, wakefulness and neurotransmitters at synaptic junctions such as, serotonin, norepinephrine and GABA (Bernal, 2015). Thyroid hormones also promote the synthesis of glutathione (redox processes) by increasing the expression of antioxidant genes (Dasgupta et al, 2007).

Epigenetic activity alters the reading of gene expression, which may be passed to offspring, without affecting the genome (Sutherland & Costa, 2003). This RNA activity is germane to phenotype, rather than DNA related genotype (associated with Mendelian genetics) and represents an environmental-gene interface. The RNA processes enable post transcriptional adjustments (epigenetic modifications associated with microRNA) and protein synthesis to occur, which is potentially reversible. Links between epigenetic modifications and diet has attracted the most attention to date. As the brain cells die, and gene expression is modified (an RNA process), the number of proteins servicing these processes also diminish. These proteins are critical for neural soma (cell bodies) to grow, however this process halts in schizophrenia. When the neural somas are small, the connectivity between dendritic spines is compromised, as the dendritic spines fall short of reaching their target synapse. Poor connectivity alters thought processes. An 18% reduction in olfactory sensory neuron proteins (English et al, 2015) might explain changes in sensory perception in schizophrenia. A deficiency in the thalamus also reduces sensory protein levels by 68% in schizophrenia (Emamian et al, 2004). This deficiency, however, is linked to cognitive changes (Zheng et al, 2012) and negative symptomatology in schizophrenia (Siuta et al, 2010).

Alterations in brain structure

Imaging studies verify that progressive architectural changes are occurring in the brain organelle of people with schizophrenia. Magnetic resonance images confirm structural changes to the thalamus (Andreasen et al, 1990). Abnormalities in the white matter of people who had schizophrenia, show cellular damage that reduces neuronal size, dendritic length and spine density, as well as, synaptic proteins (Kubicki et al, 2005). These consistent changes, affect the brain's volume and tissue (white and grey matter), in both the hippocampal and pre-frontal brain regions (Gur et al, 2007). Iron is the micronutrient required for white matter (Pinero & Connor, 2000). White matter messaging requires connectivity and the ability to

adjust action potentials. Alterations in the white matter, by the first episode of psychosis, have been correlated to symptoms domains in the corpus callosum (Positive and Negative Syndrome Scale) (Zhang et al, 2016). The volume of white matter in the brain may be a marker of its energy expenditure (Karbowski, 2007). Selenium is the essential trace element required for grey matter (Kuhbacher et al, 2014). Grey matter is responsible for cognitive processes in glial cells, neural cell bodies and synapses. These volume changes in grey matter are associated with mood and behavioural changes (Benedetti et al, 2010).

Post mortem

Besides metabolic-induced changes to brain architecture, post mortem studies reveal ongoing impairment to redox processes. The co-ordination of cell survival is reliant on the family of redox-metabolic isoenzymes, glutathione S-transferases (Klaus et al, 2013). However, on post mortem, at least the glutathione S-transferase mu (GSTM1) class remains depleted in schizophrenia, major depression and bipolar disorder (Gawryluk et al, 2011). These glutathione S-transferases are required for fine tuning metabolism, acting as thyroid hormone binders and transporters in both neurons and glial cells (Johnson et al, 1993). Glutathione S-transferases are also antioxidants, which are relevant for mitochondrial and cellular defence; to catalyse glutathione peroxidase activity, protect the cell against oxidative stress and lipid peroxidation (Yang et al, 2002). However, the glutathione S-transferase family are better known as a cofactor of glutathione, with roles in cellular detoxification processes (including heavy metals) and redox reactions. Post mortem evidence reveals ongoing impaired glutathione utilisation involving glutathione S-transferases, which persistently alter the cell's redox state (Yao et al, 2006). These ongoing impediments to redox processing continue to adversely affect the metabolic machinery that is required to support the brain's energy requirements.

Acute episodes

Stress is known to trigger acute episodes of mental illness. Moreover, in rodent models, psychological stress is shown to reduce serum iron levels (Wei et al, 2008). Serum iron levels, linked to dopamine, are reduced during acute psychotic episodes in schizophrenia (Wiser et al, 1994). Low brain iron levels are associated with changes to behaviour and cognitive processes (Pinero & Connor, 2000) such as, the speed of thought processing, learning and memory (Fretham et al, 2011). A likely explanation for this is the requirement for iron to synthesise both neurotransmission (Pinero & Connor, 2000) and the thyroid hormone production that interrelate with catecholamine and thyroamine for neuronal activity and body temperature.

The Hypothalamic-pituitary-adrenal (HPA) axis is responsible for integrating the signals needed for adaptation to stress (Smith & Vale, 2006). This HPA axis signalling mediates the disrupted thyroid hormones. Stress hormones such as, glucocorticoids help control energy supplies for metabolic requirements in response to stress (Kratschmar et al, 2012). Glucocorticoid release reduces Nrf2 activity to further suppress antioxidant defence capability (Kratschmar et al, 2012) and regulate the inflammatory and auto-immune activities linked with HPA axis abnormalities (Silverman & Sternberg, 2012). Glucocorticoids are also steroids. Steroids are linked to increases in aggressive and violent behaviours (Maycock & Beel, 1997).

DISCUSSION

There is robust evidence that schizophrenia is a metabolic disorder. This verifies the earlier approach of Emil Kraepelin to dementia praecox, although thyroid glandular and gonad extracts were ineffective (Noll, 2007); possibly because of chromatin remodelling (Secco et al, 2017). His contemporary Eugen Bleuler, was greatly influenced by the work of Sigmund Freud and later Carl Jung, who founded analytical psychology. Under the influence of analytical psychology and eugenics; psychiatric practice strayed away from neurobiology. Psychotherapy continues to influence clinical practice today.

Mental illness appears to be the expression of an adaptation to nutrient or hypoxic stress that affects cognitive functions and the ability to cope with psychological stress. Cats in the Simpson desert of Australia have red fur as an adaptation to their environment. Charles Darwin proposed that adaptation persisted if it was advantageous to species survival (Darwin, 1872). This mechanism is conserved across species as a vehicle for evolution. In plants epigenetic changes provide adaptation to reoccurring nutrient or oxygen stress through the development of a stress memory (Lamke & Baurie, 2017). Epigenetic changes to gene expression enable a memory of the stress be established in the short term. without affecting the genome. The stress memory enables adaptation to changes in their environment and also prepares the offspring for their new environment (Lamke & Baurie, 2017). This is heritable only if the nutrient stress persists and it certainly does not enhance reproductive success. The main tenant of natural selection is survival of the fittest (Darwin, 1872) to suggest a reduced ability to procreate the species. This view was underscored during a recent clinical trial in schizophrenia and affective disorder. Premature menopause was reported by 73.17% of the women enrolling onto the trial who refused pregnancy kits because of it (unpublished Laupu). Evolution is therefore closely related to phenotype (Polimeni & Reiss, 2003) changes that Darwin observed, rather than genotypic changes proposed by Galton.

These advances in our understanding of schizophrenia necessitate that we revisit the terminology we use to describe this disorder. This discussion points to a biological explanation that is incongruent with an unconscious splitting from reality. The term schizophrenia is no longer appropriate to describe this neuropathology. However, convention dictates that the term schizophrenia be used as it was the last term proposed to describe the disorder. There is also stigma surrounding the name schizophrenia which can be traced back to the eugenics movement and the brutality of psychiatrists during this time. The term, memory stress is more accurate and devoid of connotations associated with eugenics. The memory stress can be described by the most prominent symptom that is expressed. For instance, psychosis (schizophrenia), mood disturbance (bipolar), low mood (depression), anxiety or delayed anxiety (post-traumatic stress disorder).

A modern approach is required, which views the brain as an organ in the central nervous system. The brain needs specific nutrients and oxygen. Nutrients must be supplied to the brain in adequate amounts to meet the brain's energy requirements for optimal cognitive functioning. Without specific nutrients or oxygen, thyroid hormone availability and signalling is disrupted. A healthier brain supports cognitive functions and adaptation to psychological stress.

A limitation of this work is that not every paper ever written on the topic of schizophrenia was reviewed. However, sufficient work was conducted to provide us with an overview of the neuropathology involved in schizophrenia. The mechanism which is described in this discussion is relevant to clinical presentations involving psychotic thoughts, alterations in mood, speech, emotions and memory that impair cognition.

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