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Schizophrenia: A Scientific and Artistic Review

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Review

Schizophrenia: A Scientific and Artistic Review

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Schizophrenia is a neurodevelopmental psychiatric disorder affecting approximately 0.5-1% of the world's population. The symptoms of schizophrenia are positive, negative, and cognitive in nature, but the effects of schizophrenia have far more widespread effects than these. There are several causative theories of schizophrenia, including the dopamine hypothesis, glutamate hypothesis, dendritic spine abnormalities, and immune system involvement. These theories have provided proposed pharmacological targets, giving rise to numerous antipsychotic drugs. Despite the modest effectiveness of antipsychotic drugs, their systemic side effects are severe and plentiful. These side effects only add to the countless, inherent side effects that accompany this disease, the most notable of which are described in this review. Quality of life is severely impaired in schizophrenia patients, with stigma being a significantly contributing factor. This review, as well as the accompanying dance video, aim to portray the large extent to which schizophrenia affects the whole person.

Introduction

Epidemiology

Schizophrenia (SCZ) is a neurodevelopmental psychiatric disorder that impairs perception, cognition, and motivation in those afflicted.[1] This disorder's impairments reflect alterations in neuronal circuitry within and across multiple brain regions.[2] SCZ affects approximately 0.5-1% of the world's population, and beyond the individual impact has a large economic, societal, and familial burden. Schizophrenia is a highly heritable disease with a lifetime prevalence of 0.4%.[3] Its onset occurs in late adolescence or early adulthood, and over time bears progressive academic, functional, and social impairment.[4] The highest age range of incidence among men is 10-25 and among women 25-35.[5] Schizophrenia is also more commonly diagnosed in males than females (a 1.4:1 ratio) and males have poorer responses to treatment and poorer outcomes.[2] The lifespan of individuals with SCZ is reduced by over 20 years, and the primary causes of death are cardiovascular disorders, including obesity, arterial hypertension, metabolic syndrome, and type II diabetes.[6]

Symptoms

There are three main types of symptoms in SCZ: positive, negative, and cognitive.[7] Positive symptoms include bizarre trains of thought, hallucinations and delusions; negative symptoms include apathy, poor rapport, lack of spontaneity, motor retardation, disturbance of volition, blunted affect, emotional withdrawal, and passive behavior; cognitive symptoms include distractibility, poor attention, and working-memory deficits. Abnormal circadian rhythms have also been observed in patients with SCZ.[4]

Risk Factors

Risk factors for SCZ are both environmental and genetic.[1] People born in an urban environment have two times the risk of developing SCZ than those born in a rural environment. Some studies suggest that even just living in a city, regardless of birthplace, raises risk for SCZ. Moreover, migrant populations, especially ethnic minorities, face a higher risk of incidence.[8] It has also been suggested that those who chronically use marijuana during early adolescence face heightened risk as well.[7] For further risk factors, see Figure 1.[10]

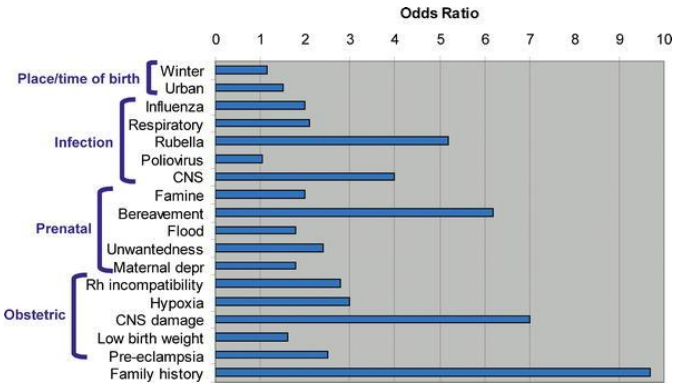

Figure 1: Environmental risk factors that increase odds of developing SCZ.[10]

Genetic risk factors for SCZ also play a role. Common allelic variants and rare copy number variants have been associated with SCZ.[11] The genetic component of SCZ is well supported as the rate of SCZ is 6-17 times higher among first degree relatives[2] and 40-50 times higher in a monozygotic twin of an affected individual compared to the general population.[12] Rates of schizophrenia among relatives of schizophrenic patients are significantly heightened (Figure 2).[10] However, the identification of specific genetic causes remains a challenge.

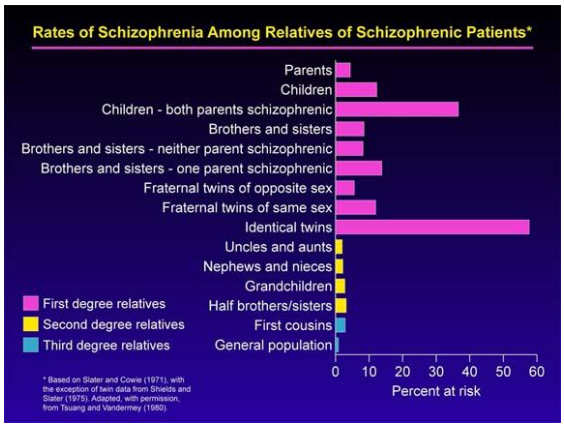

Figure 2: Percent of first, second, and third degree relatives of SCZ patients at risk for developing SCZ.[10]

Neural Abnormalities

The interaction of environmental exposure and genetic predisposition produces the effects of altered neurodevelopment that manifest in this behavioral syndrome.[2] The altered connectivity within and between multiple brain regions is the framework for the pathophysiology of this disease.

Hypotheses

There are a number of hypotheses regarding the causation of SCZ, including dopamine, glutamate, dendritic spine abnormalities, and immune system involvement. The dopamine and glutamate hypotheses are the primary causative theories, and though the exact abnormalities of these two neurotransmitters vary between the hypotheses, their effects are the same (Figure 3).[13]

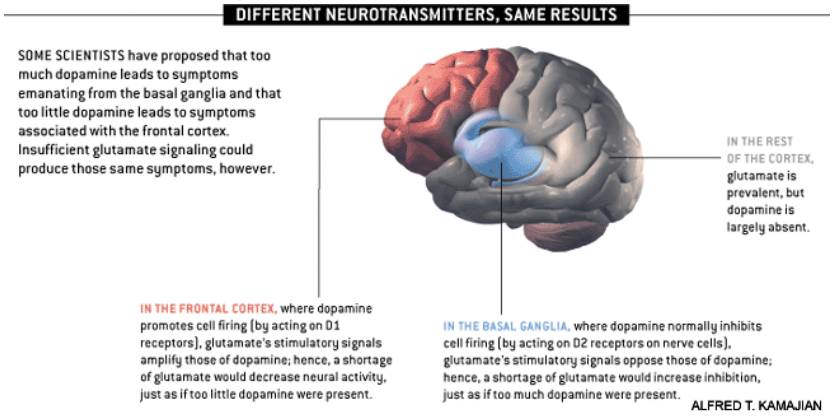

Figure 3: Effects of dopamine and glutamate on the brain in SCZ.[13]

Dopamine Hypothesis

The dopamine hypothesis of SCZ was the initial and remains the most common theory.[14] Dopamine is a neurotransmitter involved in regulating reward, locomotion, behavior, learning, and emotion. Excess dopamine transmission is thought to play a role in the pathophysiology of SCZ.[15] Dopamine belongs to the catecholamine family of neurotransmitters and is produced in the substantia nigra and ventral tegmentum.[16] While the original theory proposed hyperactive dopamine transmission, the "revised dopamine hypothesis" has offered a far more nuanced view of dopamine abnormalities in SCZ patients. The revised version of this theory proposes hyperactive dopamine transmission in the mesolimbic areas and hippocampus, hypoactive transmission in the prefrontal cortex, and general dopamine dysregulation in the amygdala and prefrontal cortex (Figure 4).

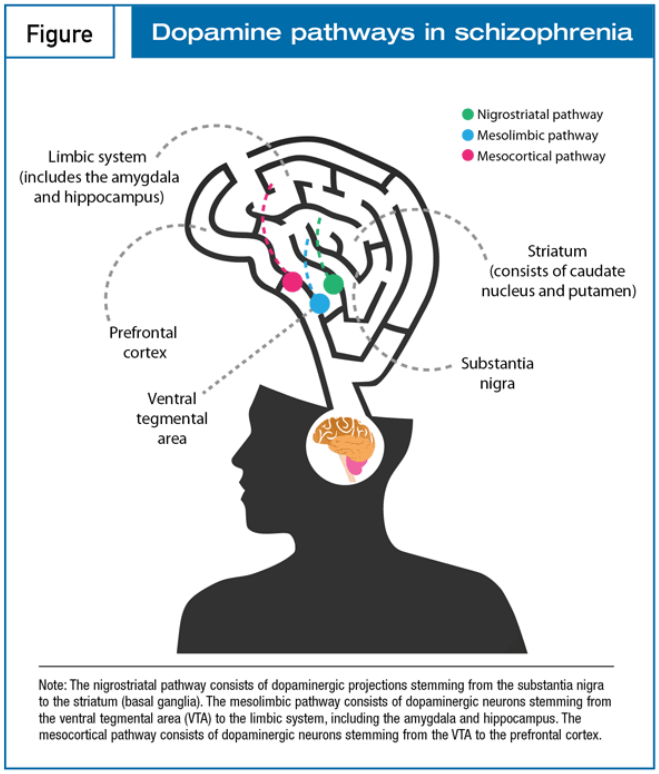

Figure 4: Brain pathways in which dopamine plays a role in SCZ.[16]

It is known that dopamine in the basal ganglia is involved in mediating motivation, learning, and action.[4] The positive symptoms of SCZ can easily be linked to dopamine hyperactivity.[7]

However, it is more difficult to link negative and cognitive symptoms to dopamine abnormalities, a limitation of the theory that has become increasingly apparent in the last 20 years and has given rise to another emergent theory: the glutamate hypothesis.[18]

Glutamate Hypothesis

The negative and cognitive symptoms of SCZ may be better linked to the glutamate hypothesis.[18] Glutamate is the most abundant neurotransmitter in the body, as well as the most excitatory. It is also the precursor for a γ-aminobutyric acid (GABA), the most inhibitory neurotransmitter. Glutamate acts on ionotropic N-methyl-D-aspartate receptors (NMDARs).

In the glutamate hypothesis, dopaminergic deficits are acknowledged only as secondary to underlying glutamatergic dysfunction. The glutamatergic model has emerged based upon observations of psychomimetic agents like phencyclidine (PCP) and ketamine. Phencyclidine and ketamine induce similar symptoms to those observed in SCZ: positive, negative, and cognitive. PCP and ketamine are non-competitive NMDAR antagonists that block NMDA-based neurotransmission. NMDARs are ionotropic glutamatergic receptors located on brain circuits that regulate dopamine release via a GABAergic neuron. Consequently, the mechanism of action and effects of PCP and ketamine can be studied to better understand SCZ.

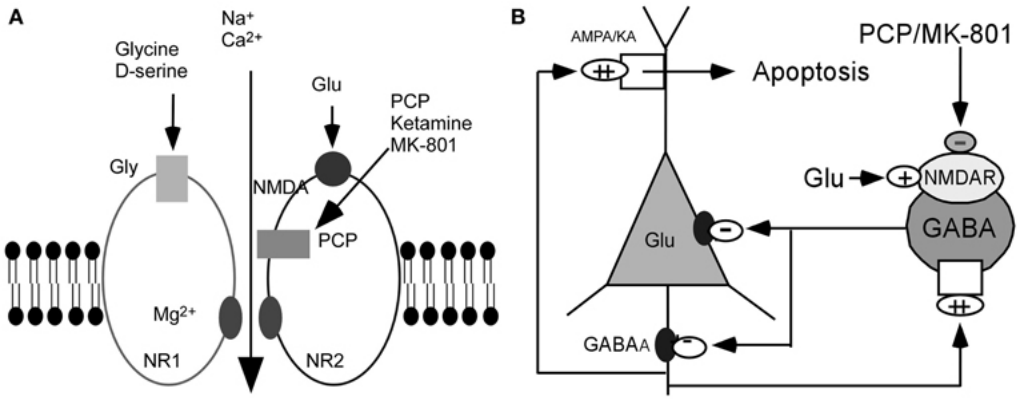

Figure 5: A. NMDAR complex. B. NMDAR hypofunction on GABAergic neurons causing excitotoxicity.[19]

The main conjecture of the glutamate hypothesis is that patients with SCZ have a deficiency in NMDARs, the receptor acted upon by glutamate. This deficiency prevents NMDARs from being properly stimulated by glutamate. This is detrimental because the proper functioning of

NMDARs is critical for learning and memory processes as well as cortical plasticity and maturation.[19] NMDAR hypofunction on GABAergic neurons causes a disinhibition of pyramidal neurons that release glutamate, ultimately causing excitotoxicity (Figure 5).

Further emphasizing the importance of NMDAR hypofunction in the cortex are the facts that less co-agonists (which are required along with glutamate to activate NMDARs) of NMDAR are observed in SCZ patients and several risk genes for SCZ are on NMDA receptor proteins.[18] NMDAR deficiency is acknowledged to be a key abnormality in SCZ.

Dendritic Spine Abnormalities

Beyond these two theories of causation, the pathophysiology of SCZ has also been attributed in part to deficits in dendritic spines (Figure 6).[2] Dendritic spines are protrusions from dendritic shafts that are the targets of axon terminals. They are the location of most excitatory synaptic connections. Though decreased dendritic spine density in patients with SCZ has been observed in multiple neocortical areas, they are best characterized in SCZ in neocortex layer three pyramidal neurons. Deficits in dendritic spines arise during development and are likely a result of disturbances in molecular mechanisms that underlie spine formation, pruning, and/or maintenance. Experimental models have shown that spine deficits are associated with impairments in working memory, attention, sensory motor processing, and sociability, all of which are cognitive symptoms of SCZ. It is proposed that antipsychotic drugs (APDs) are not a contributing factor to this lowered spine density.

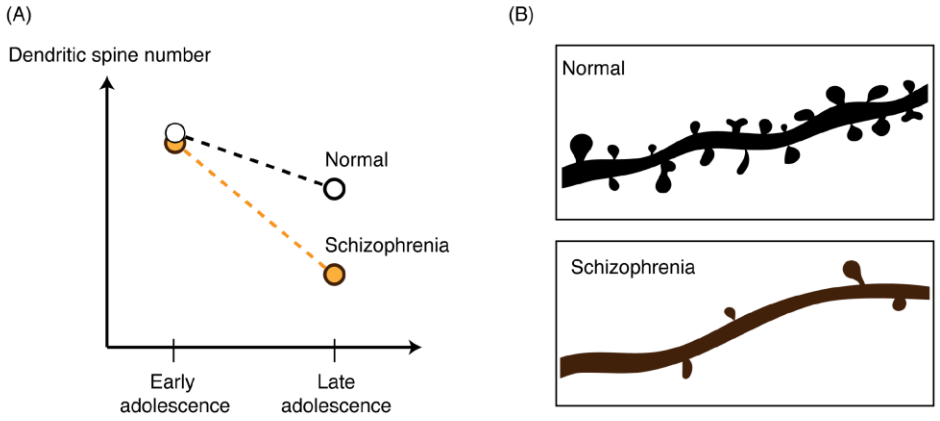

Figure 6: Dendritic spine deficiencies in SCZ.[20]

In addition to lowered spine density in layer three pyramidal neurons, other dendritic spine abnormalities have been observed in non-cortical areas like the hippocampus and striatum. In the hippocampus, the smaller volume and altered activity seemed to affect performance on some memory tasks.[21] However, studies on the morphological changes of dendritic spines in this area are mixed and preliminary.[2] In the putamen patch of the striatum, there is a higher total synaptic density of GABAergic medium spiny neurons, where cortico-limbic inputs are received.[22] This area projects to the substantia nigra pars compacta, where they inhibit dopaminergic neurons. It is hypothesized that this may be a compensatory mechanism to quiet overactive dopamine neurons.[2]

Though dendritic spines can be difficult to study because they are dynamic structures changing with varying hormone levels, environmental enrichment, drug use, learning, and synaptic activity, it is generally accepted that alterations in dendritic spines play a role in the pathology of SCZ.

There are a few molecular mechanisms that underlie altered dendritic spine density in SCZ. It is proposed that glutamate stimulation causes synaptic strengthening and an increase in spine density that is dependent upon disrupting septin barrier filament to allow potentiation.[23] Mutations to genes that prevent this (i.e. Cdc42 and Cdc42EP3) are risk factors for SCZ. Cdc42 is a RHO GTPase that is important for intracellular signaling, actin remodeling, and increasing spine formation. In contrast, Cdc42EP3 inhibits these processes. In SCZ, Cdc42 levels are lower while Cdc42EP3 is elevated, an imbalance that prevents spine enlargement and causes neuronal loss.

Another underlying molecular mechanism involves the C4 complement protein. C4 is an opsonizing protein in the classical complement pathway and is also involved in synaptic pruning as it is allowed to accumulate on neuronal spines. C4 is overexpressed and/or mutated in a SCZ brain, leading to excessive complement activation on neurons; this is an indicator for the brain volume decline observed in patients with SCZ.[24]

Immune System

In addition to the aforementioned causative theories of SCZ, genetic, biomarker, and imaging studies have shown the involvement of the immune system.[25] Though the immunological component of SCZ is only partly elucidated, the observations in this area are well founded. The increased risk of SCZ patients and their relatives for autoimmune diseases and vice versa is indicative of a deregulated, compromised central nervous system (CNS) immune process. However, it is inconclusive in postmortem studies whether there is a net effect of immune activation of the CNS.

The most notable immunological finding in the meta-analysis conducted by van Kesteren et al. is that of increased microglial density in SCZ.[25] Microglia are myeloid cells that have entered the CNS during embryonic development. They migrate to the site of an injury, such as infection, acute trauma, or neurodegeneration, to proliferate. Psychological stressors early in life and adulthood can cause elevated microglial activity, especially in the hippocampal regions. In childhood increased microglial density is associated with an increased risk of developing psychotic disorders in young adulthood.[26]

Other immunological abnormalities include an increased frequency of seroconversion (the time period when specific antibodies develop and become detectable in blood to certain pathogens) in patients with SCZ, as well as an upregulation of pro-inflammatory genes, including interleukin (IL) 1β**,** IL-6, and TNFα.[25] This increase in pro-inflammatory gene expression as well as microglial density is more pronounced in the temporal cortex, where higher order emotional processing and sensory and cognitive integration take place.

Though these causative theories vary in their approach and focus, they all play an integral part in piecing together the puzzle of this disease. They also help elucidate important targets for new treatments and therapies.

Treatments

Antipsychotic drugs were first introduced in the 1950s.[25] Their major mechanism of action is as agonists of D2 receptors.[27] As such, they tend to suppress positive symptoms but have little

effect on the cognitive or negative symptoms of SCZ.[2] Antipsychotic action occurs when more than 65% of striatal D2 receptors are occupied by the drug.[27] Antipsychotic drugs cause many of the negative metabolic side effects that will be discussed in the next section.[6] Though APDs have improved and second-generation drugs have fewer metabolic side effects than first-generation medications, many patients struggle with APD induced weight gain and its downstream effects on metabolism. Beyond their metabolic consequences, APDs have wide ranging effects on the whole body, including myocarditis, cataracts, movement disorders, elevated prolactin levels, sexual side effects,[28] and decreased fertility.[3] Non-adherence to treatment regimens is as high as 50% in SCZ patients.[29] There is clearly a need for new biological targets and therapeutics.[2]

Beyond medication, lifestyle interventions could help ease the symptoms of SCZ.[29] With help, many of the social factors that exacerbate schizophrenia could be ameliorated. Such factors include leisure-based physical inactivity, poor diet, lower education, poverty, smoking (which is as high as 75% in patients with SCZ) and substance abuse. Potential therapies for future exploration to work to this end include fitness training, microbiome treatment to change energy intake and metabolism to impact dopamine levels, chronobiologic interventions to adjust the day/night cycle of patients to match actual day/night cycles, and increasing energy expenditure through sport in order to increase dopaminergic signaling.[4]

Pathophysiological Consequences of SCZ and Its Treatment

Schizophrenia, though a neurodevelopmental disorder, impacts far more than an afflicted individual's brain. This review aims to explore the various effects of SCZ on the whole body to better understand the disease and the burden it imposes on patients. Furthermore, it is a goal of this review that in compiling the extensive effects of SCZ on the whole body, and portraying those both scientifically and artistically, that both medical professionals and the general public may regard SCZ and those it affects with greater understanding, compassion, and urgency to find solutions.

Obesity

There is a strong correlation between SCZ and obesity. A study by Allison et al. found that 42% of a group of individuals with SCZ are obese compared with 27% of the general population.[28]

Obesity in patients with SCZ can partially be accounted for by an unhealthy lifestyle and personal genetic profile. However, antipsychotic drugs, especially second-generation ones, contribute to the prevalence of obesity in 40-60% of people receiving medication.[29] There is a typical weight gain of 3.8kg in drug-naïve patients after starting antipsychotic treatment in the first three months of treatment.[30]

Proposed Mechanisms of Action

The mechanism of antipsychotic induced weight gain is fairly well-understood. One mechanism of action relates to the antihistaminergic properties of many APDs.[29] Olanzapine, which has the highest affinity for histamine receptors,[29] and clozapine block histamine H1 and H2 receptors.[4] This weakens histamine-mediated satiety signals in the hypothalamus where histamine helps relay satiety and hunger signals. This is not the sole mechanism, however, because even drugs that don't have antihistaminergic properties cause weight gain. As such, there is a consensus that antipsychotics, though diverse and numerous, share antagonistic action on the D2 receptor, which blocks phasic dopamine effects in the striatum and other parts of the brain. This disrupts glucose regulation and has two effects on behavior: first, decreased motivation to move, and second, increased motivation to ingest a high-caloric diet.

Another potential explanation for the prevalence of obesity in mentally ill patients (not just SCZ) is altered reward anticipation, which is in turn related to striatal dopaminergic dysregulation.[4] Striatal dysfunction is supported as one of the core pathological features of SCZ and provides a link between weight gain and SCZ. Neuroimaging techniques show decreased striatal activation in drug-naïve and un-medicated patients. These are the same participants at high risk for psychosis. Reward anticipation is the dopamine response induced after the input of a conditioned stimulus that signals incentive. For example, a rodent that received a food pellet after pushing a button; prior to learning the striatum and dopamine neurons respond to getting the reward (or food pellet in this scenario), whereas after learning the striatum responds to the conditioned stimulus (or pushing the button). Because there is a reduction in striatal D2 receptors found in pathologically obese participants, similar to patients with SCZ and other addiction disorders, it is suggested that reward anticipation is decreased. Individuals compensate for this by eating impulsively, causing significant weight gain.

The degree of reduced reward anticipation is linked to symptom severity and altered dopamine activity because treatment with antipsychotics partially normalizes this dysfunction. It should also be noted that chronic changes in eating (a high-fat, high-sugar diet) can cause down-regulation of D2 receptors in animals.

Another mechanism of weight gain in SCZ is explained by in the neuro-endocrine model.[29] This suggests that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis causing higher than normal serum cortisol results in less circulating levels of leptin. A decrease in leptin, responsible for signaling satiety, leads to increased appetite, weight gain, excessive accumulation of visceral fat, insulin resistance, and dyslipidemia. A genetic rationale for weight gain in SCZ is supported by the statistic that 50% of patients with SCZ have a familial history of type II diabetes (T2D) versus 4.6% of non-affected individuals. One explanation for this is that fetal alpha-melatonin stimulating hormone (thought to be a determinant of early fetal growth) is abnormally high in infants of people with diabetes. As such, this is thought to be an independent risk factor for SCZ via its effects on brain development and maturation. An alternative explanation is that a gestational zinc deficiency causes damage to organism that have a high zinc requirement, like the pancreas, which plays a large role in digestion and gastrointestinal health.

Antipsychotic Drug Associated Weight Gain

Olanzapine is the first line treatment for first episode SCZ.[6] However, in a meta-analysis done by Allison and Casey, patients being treated with olanzapine had a mean weight gain 4.15kg over the course of 10 weeks, second only to the 4.45kg weight gain observed with clozapine.[28] Of the second-generation APDs, olanzapine and clozapine are the two most commonly associated with diabetes. In a study by Koro et al. using the United Kingdom General Practice Research Database, of the 18,903 individuals with a diagnosis of SCZ those who received olanzapine had significantly increased odds of developing hyperlipidemia compared to those who didn't receive any APDs and those who received a first-generation APD.[31] Another study showed that time of treatment with olanzapine advanced time of diabetes onset.[6] If giving during the first year of antipsychotic treatment, olanzapine was associated with a significantly shorter time to diabetes onset versus when given during the development of diabetes when it was not associated with an

increased risk of diabetes. This altered trajectory can be explained by initial weight gain that adversely affects insulin resistance, or direct effects on pancreatic beta cells that cause a quickened diabetes onset in vulnerable individuals.

Despite the well supported link between drugs like olanzapine, clozapine, and low potency first-generation antipsychotics and diabetes, three months after the onset of diabetes the overwhelming majority of patients were still on those same high-risk drugs; only 6% switched to low-risk drugs.[6] Of the patients diagnosed with diabetes, only 26.1 had been treated with one of the two low-risk drugs (aripiprazole and ziprasidone) prior to treatment with the high-risk drugs. These studies bring into question practitioners' use of olanzapine as their first line treatment.

Co-occurring diseases that contribute to obesity in SCZ include hypertension, coronary artery disease, osteoarthritis, type II diabetes mellitus, and stroke.[28] Type II diabetes (T2D) in patients with SCZ is 2-4 times greater than the general population.[29] It has a prevalence in SCZ patients between 10.8% and 14.9%, with an increased prevalence in older individuals, females, African Americans, and other non-whites. There are 41% of people under age 44 with a dual diagnosis of SCZ and diabetes, compared to just 30% of people under age 44 with just diabetes. 19% of people with dual diagnoses SCZ and diabetes died prematurely versus 9% with just diabetes. There's even an increased risk for diabetes in first-degree relatives of those with SCZ. Beyond diabetes, 1 in 2 patients with SCZ are overweight, 1 in 5 have significant hyperglycemia, and at least 2 in 5 have lipid abnormalities.[30]

Metabolic Syndrome

Another co-occurring condition that co-exists with the other weight-related diseases discussed above is metabolic syndrome (MetS).[29] Metabolic Syndrome is a cluster of risk factors including hyperglycemia, dyslipidemia, hypertension, a prothrombic state, and central obesity,[29] the presence of three or more of which are symptomatic of having the disorder.[30] Almost 1 in 3 patients with SCZ suffer from MetS. The rate of incidence is 50% (two- to three-fold higher than the general population) in people with severe mental illness.[29] The explanation for the prevalence of MetS in people with severe mental illness, including SCZ, is likely multi-factorial and includes environmental, genetic, lifestyle, and iatrogenic contributions. MetS is predictive for

cardiovascular disease, which will be expounded upon later in this review.[30] The effects of SCZ do not stop with the cardiovascular system though, its consequences are far more widespread.

Other Full-Body Effects

Fertility

Further investigation of the full body effects of SCZ lead to another important finding discussed extensively in a review and meta-analysis by Bundy et al., that of reduced fertility in patients with SCZ.[3] Studies have found that in SCZ patients males have significantly fewer offspring than females. These abnormal fertility rates extend beyond the patients themselves, affecting relatives of SCZ patients as well. Siblings of patients have lower offspring compared with the general population, with the decrease in brothers being more prominent than in sisters. Results are somewhat inconsistent when it comes to studying the fertility of parents of patients with SCZ. A few reasons for the decreased fertility in SCZ patients include availability of sexual partners, emotional and social functioning, sexual desire and reproductive health, psychotropic medications, and drug, alcohol, and tobacco misuse. The disproportionate effect on men's fertility is thought to be attributed to their earlier age of onset and poorer outcomes as well as poorer premorbid function prior to SCZ onset, thus limiting opportunities for potential parenthood. Taken in conjunction with the genetic component of SCZ already discussed, we arrive at a dilemma that has been coined the "Schizophrenia Paradox," which raises the question of how genetic variants predisposing individuals to SCZ are maintained in the population despite imposing reduced biological fitness. There are a few proposed mechanisms that could aid in explaining this paradox. First is the generally accepted idea that SCZ is under polygenic control. Following this line of thinking, there is potentially a set of loci that together influence disposition to paranoid thinking, which, if fall at one extreme of the phenotypic spectrum, will put an individual at greater risk of developing the disease. The association between SCZ and older paternal age suggest that some cases of SCZ may be due to de novo mutations in the male germ line. Rare copy number variations (CNVs) have also emerged as a risk factor in some cases of SCZ. These de novo mutations arising from both the male germ line as well as inherited from recent ancestors may help explain the heritability of SCZ despite poor biological fitness.

Hypothalamus

Abnormalities in gonadal and adrenal hormone levels point to hypothalamic structure abnormalities in SCZ patients, more specifically an enlarged hypothalamic volume (Figure 7).[32] This enlargement is most notable in mammillary bodies and the paraventricular nucleus (PVN). Rates of dysfunction range between 50% and 70% and manifest in endocrine and stress-response dysfunction, such as anxiety. This enlargement is more prevalent in women than men, more severe in multiplex than simplex cases, and more pronounced on the right side. The hypothalamus is also significantly larger in nonpsychotic first-degree relatives of SCZ patients, an observation that is also stronger in multiplex cases. The enlarged hypothalamus in SCZ patients and their relatives is important in explaining endocrine abnormalities that accompany SCZ.

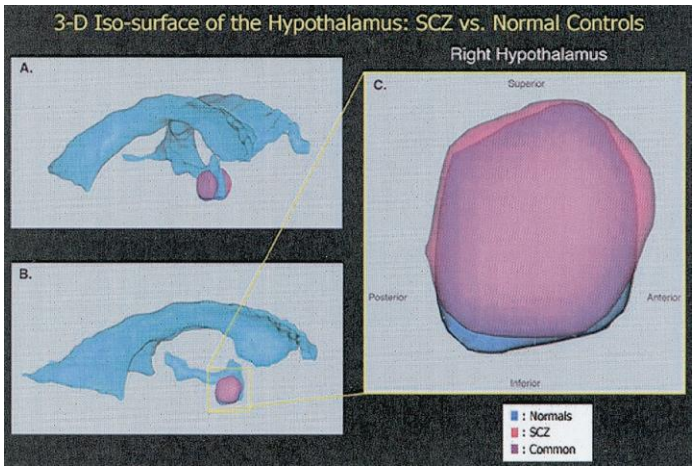

Figure 7: Hypothalamic enlargement in SCZ.[32]

Potential explanatory models for this phenomenon include increased number of hypothalamic neurons, neuron size, or increased neuropil resulting from disruption in normal brain development. This could be attributed to disrupted aromatization of testosterone to estrogen, affecting both males and females via a similar mechanism. Developmental apoptosis is regulated in part by testosterone and estrogen, so the disruption of aromatization mid-gestation will result in less hypothalamic apoptosis and an increased number of neurons. This same effect is observed in women with SCZ where a disruption in the hypothalamic-pituitary-gonadal system is often

observed, resulting in the high androgen and low estrogen levels that alter normal developmental apoptosis.

Paraventricular Nucleus

Continuing in this extensive review article, Goldstein et al. discuss the enlargement of the PVN that also has many implications on the endocrine systems of patients affected with SCZ. In the PVN there is a high density of cortisol releasing hormone (CRH) neurons that also release norepinephrine (NE) as part of the stress response. Cortisol releasing hormone neurons are co-localized with estrogen receptors (ERs), thereby suggesting the ERs play a role in PVN release of CRH. In major depression, an increase in hypothalamic volume as well as CRH neurons co-localized with ERs was also observed, which may have implications in understanding SCZ. Moreover, abnormalities in the number of vasopressin and oxytocin neurons and hormone levels have been observed in SCZ regardless of APDs.

Thyroid

Another endocrine abnormality found in patients with SCZ is related to thyroid hormones. Psychotic symptoms, many of which resemble those in SCZ, may occur in patients with both sever hypo- and hyperthyroidism.[33] In a study, serum thyroxine (T4), triiodothyronine (T3), reverse triiodothyronine (rT3), and thyroid stimulating hormone (TSH) levels were measured before and after 4 weeks of treatment with perazine, a phenothiazine derivative. The sample included 31 acutely ill patients, 19 SCZ patients in remission receiving no medication, 20 SCZ patients in remission taking medication, and 24 patients with residual-type SCZ. The only notable abnormalities in these hormone levels were observed in acutely ill patients. At the study's start, levels of T4 were elevated, but levels of the other three hormones were normal. T4 is correlated with severity of illness and degree of response to neuroleptic treatment. There was a significant fall in both T4 and rT3 in the fourth week, a decrease that was correlated with clinical response. This suggests that neuroleptic medications may affect thyroid hormone metabolism in acutely ill SCZ patients.

Other Co-Occurring Conditions

There is a strong, bidirectional relationship between SCZ and epilepsy.[5] The risk of seizure disorders is five times higher among children with psychiatric diseases. A study by Chang et al. showed that epilepsy was almost six times higher among both children and adults with SCZ. One can turn to the shared susceptibility for these two diseases to explain this co-occurrence. Both share the same candidate genes, including the leucine-rich glioma inactivated 1 (LGI1) gene, which is involved in neurodevelopment and associated with febrile seizures and SCZ, as well as the CNTNAP2 gene, which is important in organizing myelinated axons but may disrupt neuroblast migration. Other environmental and neurobiological factors (i.e. cortical dysgenesis or diffusive brain damage) may also be contributive.

Cardiovascular Disease as the Leading Cause of Death in Schizophrenia

There is a three-fold increase in mortality rates in SCZ compared to the general population.[34] While the elevated risk of suicide and accidental death were previously reported to be the primary causes of premature death in SCZ, more recent work suggests premature mortality is due to cardiovascular disease. This is attributed to the higher prevalence of factors that heighten CHD risk, including smoking, unhealthy diet, physical inactivity, obesity, diabetes mellitus, hypertension, low high-density lipoprotein (HDL) cholesterol, lower quality primary chair, and APD induced weight gain. Diabetes mellitus is a particularly strong risk factor for cardiovascular mortality at a risk level approximately equal to that of a myocardial infarction.[6] An increased or decreased risk of CHD is associated with particular APDs; olanzapine is associated with a 0.5% increase, quetiapine 0.3%, perphenazine a decrease of -0.5%, risperidone -0.6%, and ziprasidone -0.6%.[27] These differences are attributed primarily to changes in HDL cholesterol levels.

Cardiovascular disease has far reaching effects beyond their direct consequences on the cardiovascular system. Cardiovascular risk factors are also important risk factors in the development of dementia and other cognitive decrements, further speaking to the far-reaching, full body effects of SCZ.[35] There is already an established relationship between high BMI and hypertension resulting in poorer cognitive performance even without SCZ[36], but when diagnosed with both BMI/hypertension and SCZ cognitive performance worsens still.[35] In studies examining this relationship, it was found that having just SCZ had a negative effect on all

measures of cognitive performance. A combination of SCZ and high BMI was modestly associated with worse verbal memory performance, though not at statistically significant levels. A combination of SCZ and hypertension, however, caused significant negative effects on immediate, delayed, and recognition memory, an overall poorer verbal memory performance; hypertensive SCZ patients performed significantly worse than their non-hypertensive counterparts.

The proposed mechanism of action is related in part to atherosclerosis, as supported by the correlation between dementia and atherosclerosis severity. Other proposed mechanisms are nonvascular in nature. For obesity, it has been suggested that the direct action of adipocytes on neuronal tissue by releasing neurochemical mediators is a contributing factor.[37] Leptin is another proposed mechanism. Leptin facilitates learning, spatial memory, and long-term potentiation.[38] It is also shown to enhance NMDAR function and modulate hippocampal synaptic plasticity.[39] Higher levels of leptin are associated with high BMI.[40] Leptin resistance, therefore, may provide the link between obesity and poor cognition.

For hypertension it is thought that increased activation of the renin angiotensin aldosterone system (RAAS) may be a factor linking this condition to cognitive impairments.[41] RAAS is activated when blood pressure is low and works to increase blood pressure by releasing hormones that promote water retention. Observations of mice show that increased RAAS activation impairs cognitive function and is ameliorated by angiotensin II type 2 receptor antagonists. Oxidative stress is another underlying mechanism that has been proposed.

Quality of Life Issues

Even in SCZ patients who are relatively healthy, concerns regarding quality of life (QOL) have been of increasing concern in recent years.[42] Various studies have aimed to study quality of life in patients with SCZ. Such studies have found that the presence of positive and negative symptoms is correlated with poor QOL. Higher medication adherence, despite the negative side effects of many APDs, is associated with better QOL. The de-institutionalization movement of psychiatric patients that started in the 1960s has had significant impacts on QOL. At its start, this movement inadvertently caused many psychiatric patients to be homeless or in jail and made

many patients victims of assaults or suicides. If patients did have family to help them, home care was often too difficult and intensive for families to maintain. Though these are still relevant and prevalent problems, new APDs and halfway houses have helped offer a better avenue for psychiatric patients to improve their QOL.

Stigma

Accompanying these quality of life concerns are the pervasive negative societal attitudes towards SCZ patients constituting stigma.[43] Stigma is described as "a deeply discrediting attribute that reduces the bearer from a whole and usual person to a tainted, discounted one."[43] The bearer is usually seen as not having legitimacy to participate in social interactions, in part because he/she is perceived as dangerous and unpredictable. Though stigma varies across cultures, it is generally observed that SCZ patients experience a high level of stigma, which restricts many aspects of life. Common impacts of stigma include social exclusion, unsatisfactory housing, and restricted opportunities for employment and education. All of these severely decrease QOL. Stigma does not always come from external sources; self-stigmatization has a significant impact (both positive and negative) on self-esteem and self-efficacy.[44] There is an inverse relationship between having a paid job and experiencing stigma. This may be due to the greater degree of self-esteem resulting from SCZ patients being ensured a job. Second, patients who achieve a higher level of functioning experience lower self-stigma, anticipated stigma, and participatory restriction. Third, knowledge (or lack of) about diagnosis and treatment for patients with SCZ influences the alienation component of stigma. As such, simple psychoeducation may help lessen stigma and improve QOL.

Schizophrenia Expressed Through Art

The arts have always been a means of communication, and in recent years have become an increasingly favored medium for the communication of scientific information.[45] This is effective in that it targets the affective rather than the cognitive domain of learners, encouraging creativity by intuitive thinking and promoting more meaningful social change through public behavior, action, and attitude towards an issue.

Review

With its power to convey difficult social issues, the accompanying dance video aims to encourage such creativity, eagerness, and compassion with regard to SCZ. This video began as a collaborative project between colleagues who contributed to its creation through their videography and creative input. The aforementioned aspects of SCZ, particularly symptomology and quality of life struggles, are those that are conveyed artistically through the accompanying dance video and music. The movement and music portray the story of a young woman at the onset of her SCZ and the subsequent havoc it wreaks on not only her psyche but her whole person.

It is clear that there is a need for better treatments for those plagued with SCZ. This need for treatment improvements extends far beyond actual medical treatments that must be enhanced to minimize adverse side effects and into the way that SCZ patients are treated in social and political contexts. It is the aim of this review that by spreading knowledge of the physiological basis of SCZ and expressing its full body effects through art that better understanding, humility, and compassion for SCZ patients may be garnered by its readers.

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