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A Review of the Models of Schizophrenia: And a putative novel, more unified model

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Abstract

Schizophrenia is a debilitating disease state which causes immense pain to sufferers and to their families. Although some proximate causes of symptoms of the disease have been identified, no ultimate cause has been uncovered which can explain all of the symptoms. This paper presents a novel theory of the ultimate cause of some forms of chronic schizophrenia with the potential to explain many (if not all) symptomologies associated with the disease. In addition to its explanatory power, this putative model may also give rise to new early diagnostic tools and treatments for schizophrenia. After the model is fully explained, suggestions for further research to confirm this model's validity are put forth.

Introduction

Schizophrenia is a disease which is part of the set of human psychotic disorders and which affects about 1% of the population worldwide. This disease has been shown to have a strong genetic component, with a heritability of around 80% (Rapoport et. al., 2005). Although the genetic basis of schizophrenia is well established, the details surrounding the specific loci of inheritance are sparse save that there are likely to be multiple loci involved instead of just a single gene (Kopala et. al., 2001). Likewise, the physiological basis of the onset of psychosis is unknown (Duncan et. al., 1999). Despite the lack of ultimate certainty in the underlying causes of this disease, several models have been proposed in the literature thus far.

One such model is the *N*-Methyl-D-Aspartate (NMDA) hypothesis of schizophrenia. NMDA is a specific agonist for a subset of glutamate receptors called NMDA receptors, which help to regulate the membrane potential of the cell (Haack et. al., 1990). The NMDA model hypothesizes that the hypofunction of NMDA receptors is the underlying cause of schizophrenia. This model was proposed because the actions of ketamine and phencyclidine (PCP) can both cause and exacerbate psychotic symptoms

similar to schizophrenia, and both block NMDA receptor activity. The hypofunction of NMDA receptors could in theory generate a pattern of dopaminergic dysregulation which could in turn further negatively impact NMDA systems (Laruelle et. al., 2003). These irregularities in the dopamine system, which are accounted for in the proposed theory below, could lead to decreases in nitric oxide levels because NMDA receptor stimulation results in calmodulin mediated increases in nitric oxide synthase [and in turn nitric oxide] (Coyle, 2013). Since nitric oxide mediated vasodilation is central to the theory proposed in this paper, the above points render the NMDA hypothesis largely subsumed by the proposed model. Although the NMDA hypothesis accounts for several facets of the schizophrenic disease state, it is inadequate as it has several shortcomings. For example, one important shortcoming of the NMDA model is that it fails to explain the lack of power of agents that reduce the toxicity of NMDA antagonists in the treatment of schizophrenia when used alone (Olney et. al., 1999). These shortcomings necessitate the exploration of a second model.

A second model of schizophrenia is the dopamine hypothesis. This model hypothesizes that the onset of the disease is characterized by abnormal dopamine

processes. In its current form, a hypodopaminergic state occurs in the frontal regions, causing negative symptoms, while a hyperdopaminergic state in the ventral tegmental area results in psychosis (i.e., positive symptoms). There are numerous shortcomings of the dopamine hypothesis, including a lack of evidence of abnormally high dopamine levels, along with the low affinity for dopamine receptor subclasses of certain anti-psychotics (Duncan et. al., 1999). Additional shortcomings include the fact that some anti-psychotics, such as Haloperidol, actually significantly increase dopamine receptor binding potential when used long term (Silvestri et. al., 2000). Despite these failures, the dopamine theory is currently still a predominant theory, and is subsumed by the model proposed in this paper with modifications which make up for many of its shortcomings. For example, the model proposed in this paper includes an alteration in the ratio of D1/D2 receptor activity. This does not necessitate an overall increase in either dopamine receptors, metabolites, or dopamine itself. Again, the shortcomings of the dopamine hypothesis necessitate the exploration of a third model of schizophrenia.

A third model of schizophrenia is the attentional or information processing model of schizophrenia. This model draws from the above neurotransmitter models with a focus on the attentional component of the disease. Evidence for this model comes from several sources, including work by Takahashi et. al. (2010) which states that schizophrenics cannot effectively gate irrelevant sensorimotor and cognitive information, and which shows neural substrates for accompanying (and perhaps proximately causal) deficits in mismatch negativity (MMN) and P3a in schizophrenics. These neural substrates implicate widespread attentional network abnormalities in the

brains of schizophrenics. Further evidence comes from work by Swerdlow et. al. (2008) which suggests that, in humans and in mice, NMDA antagonists can disrupt pre-pulse inhibition (PPI). Incidentally, PPI is also reduced following the administration of phencyclidine (PCP), which is used to create a model of schizophrenia commonly used in experimental animals. The information processing deficits seen in this model can be accounted for by an alteration in the D1/D2 receptor activity ratio. Because such an alteration is incorporated into the proposed model in this paper, the information processing model of schizophrenia is subsumed by the model proposed in this paper.

A final model of schizophrenia, the PCP model, is also subsumed by the model proposed in this paper. The PCP model of schizophrenia is based on the fact that the induction of psychosis can be achieved by administering PCP. This induction of psychosis may be in part mediated by cardiovascular system effects of the drug. This is supported by the fact that rats given PCP have changes to their electrocardiogram completely blocked by either Haloperidol (an anti-psychotic effective in treating schizophrenia) or the vasodilator agent nitroglycerine (Shi & Xu, 1994). This suggests that the efficacy of Haloperidol in treating schizophrenia is partially mediated by the ultimate effects of its administration on the cardiovascular system (see later explanation of these effects and the drug's efficacy). This also suggests that the effects of PCP are in part mediated by cardiovascular effects. Additional support for this concept comes from the fact that in rats nitric oxide (NO) mediates vasodilation, which is effected by oestrogen and also is shown to increase after PCP administration (Palsson et. al., 2010). This response appears to be compensatory, as it is

temporally shifted with respect to the maximum behavioral effects of the drug. Interestingly, this effect occurs most in the prefrontal cortex and ventral hippocampus, two areas implicated in schizophrenia. The combination of all of the above information provides further support for the putative model put forth in this paper by suggesting the role of cardiovascular deficits having a role in the ability of PCP to create a model of schizophrenia in individuals to whom it is administered. Thus, there is the possibility that the model which will be proposed in the subsequent section subsumes the PCP model of the disease. This potential is supported by the work of Palsson et. al. (2010), which states that there is support in their data for "an interaction between PCP and a stress response converging on the NO signaling pathway."

Unfortunately, none of the neurotransmitter models currently proposed adequately account for the symptomology, progression, and treatment of chronic schizophrenia. Thus it is necessary to propose a new model which has an underlying cause not based in neurotransmission itself and which integrates the strengths of current hypotheses while accounting for their shortcomings. The model proposed in this paper fulfills this role for chronic forms of schizophrenia (it does not attempt to account for more acute forms of the disease). An outline of the proposed model, as well as supporting evidence, will be explored in the next section.

Proposed Model

Several observations in schizophrenics prompted the model of schizophrenia proposed here. First of all, although micro-level events occurring in the brains of schizophrenics would not be detectable with

the spacial resolution of imaging techniques such as magnetic resonance imaging (MRI), they may manifest on a macro level as gross structural abnormalities. Such macro level abnormalities are apparent in many MRI studies, including Rupp et. al. (2005). Secondly, impairments in vasodilation in schizophrenics have been found in several studies, including Turenne et. al. (2001) and Hudson et. al. (1997). Third, schizophrenics have increased levels of nitric oxide synthase (NOS, the enzyme which catabolizes nitric oxide) in the cortex (Karson et. al., 1995), which may be an attempt to compensate for impaired vasodilatory response to nitric oxide (like that seen in those with oestrogen resistance). Fourth, schizophrenics respond positively to treatment with oestrogen (Hafner, 2003), and tend to have low blood oestrogen levels (Rossler & Hafner, 1993). Fifth, women tend to develop symptoms of schizophrenia during points in the menstrual cycle with lower oestrogen levels. This effect was so marked that "menstrual psychosis" was listed as a separate diagnostic category in the early 1900s. This effect is mirrored across the female life cycle, as late onset schizophrenia (after age 40-45) is much more prevalent in females than males and is associated with a loss of ovarian functioning starting at about the same age (Rossler & Hafner, 1993). Finally, individuals (including non-schizophrenics) with oestrogen resistance tend to exhibit deficits in nitric oxide mediated vasodilatation, especially in response to ischemic events (Faustini-Fustini et. al., 2009). These observations, when considered simultaneously, suggest a oestrogen mediated deficiency in vasodilatory response to ischemic stimuli in schizophrenics. This deficiency may result in micro-ischemic events, micro-infarct, and general functional instability at a micro circuit level. This may be further

exacerbated by the impaired glucose tolerance (IGT) of medication naive first episode schizophrenics reported by Collins et. al. (2003) as IGT has been associated with increased risk of ischemic stroke (e.g., in diabetes). This suggestion of micro-ischemic events and micro-infarcts in schizophrenics, mediated by an oestrogen influenced deficiency in nitric oxide mediated vasodilatory response to ischemic events, forms the core of the novel putative model proposed here to account for the deficits and abnormalities seen in chronic schizophrenia.

This model has surprisingly great explanatory value as a putative ultimate cause of some forms of chronic schizophrenia. For example, the observed levels of higher neural noise in schizophrenics can be explained with this model if there are differential effects of unstable oxygen supply on D1 vs. D2 receptor systems, as the D1/D2 activation ratio is crucial for maintaining stability of the representations of internal and external stimuli in local circuits and for optimizing noise levels in these circuits (Winterer et. al., 2004). Such differential effects on D1 and D2 receptor activity after ischemia is seen in Mongolian gerbils, and consists of a decrease in the number of D2 binding sites in the striatum along with an accompanying decrease in D1 receptor affinity which is more widespread (Chang et. al., 1993). If these changes generalize to humans, they provide a putative mechanism for the alteration in D1/D2 receptor activity ratio. Further, since D2 agonists exert neuroprotective effects in rats by decreasing neuronal activity levels (O'Neil et. al. 1998), this change in the number of D2 receptor binding sites (if it generalizes to humans) may provide a positive feedback mechanism for increasing the likelihood of future ischemic events as decreasing the number of

D2 binding sites would be the functional equivalent of a D2 receptor antagonist. Indeed, such a relationship between disturbed dopamine production and an increase in the risk of ischemic stroke is strongly suggested by the observed increase in ischemic stroke in Parkinson's disease patients (Chang et. al., 1993). If this holds in schizophrenics, it would create a positive feedback mechanism such that each ischemic stroke increases the likelihood of another, thereby ensuring chronically high neural noise levels in this population.

The increase in neural noise levels generated in this manner may help to explain the decoupling between physiological markers and behavioral outcomes observed in schizophrenia. One example of this decoupling is the finding that larger left temporal lobe volumes were associated with better odor identification in controls but not in schizophrenics (Moberg et. al., 2006). A second example of this decoupling is the finding by Kayser et. al. (2010) that olfactory event-related potentials (ERPs) were substantially less related to odor intensity and subsequent identification in schizophrenics (vs. controls). A third example of this decoupling is the possible disassociation reported by Manor et. al. (1999) between attentional allocation (visual) and eye fixation location in schizophrenics. A final example of this decoupling is the fact that the correlation between olfactory bulb volume and olfactory abilities in healthy subjects (independent of age), reported by Buschhuter et. al. (2008), is not present in schizophrenics (c.f., Turetsky et. al., 2003). The wide range of domains in which this decoupling is found suggests a global level parameter is disrupted in schizophrenia. Alterations in levels of neural noise certainly conform to this suggestion.

The increase in neural noise levels generated by the alteration of D1/D2 receptor activity may also help to explain the deficits in olfaction present in schizophrenics, because according to signal detection theory this should decrease sensitivity and increase rates of false alarms of odor presence (i.e., hallucinations). This increase is consistent with the olfactory hallucinations experienced by some fourteen percent of patients (Stevenson, 2013). These deleterious effects of neural noise on olfaction should be amplified by causal fluctuations in blood oxygen level putatively experienced by schizophrenics, as these may reduce the reliability of neural responses further by limiting the resources available to make the optimal response.

In addition to this explanation of olfactory deficits, the model put forth in this paper also explains a second abnormality which could contribute to the olfactory deficits in schizophrenia. This abnormality, identified by Turetsky et. al. (2003), is that schizophrenics exhibit increased protein expression of Growth Associated Protein 43 (GAP-43). This suggests that schizophrenic patients have difficulty establishing or maintaining synaptic connections between the olfactory bulb and epithelium. The unstable oxygen supply assured by the proposed model would certainly increase the difficulty in maintaining viable connections between these two locations, and could thus help to explain the results found. Since the olfactory system depends on memory to compare odors, the high vulnerability of the hippocampus to ischemic damage would further mediate deficits in olfaction under this model. Such damage would also explain the verbal memory deficit present in schizophrenia.

The model proposed in this paper would also account for the attentional deficits that

have been recently more prominently associated with schizophrenia (e.g. Swerdlow et. al., 2008; Takahashi et. al., 2010). Thus, the attentional model of schizophrenia is subsumed by the proposed model. This attentional phenotype could be explained by the fact that attentional maintenance requires energy, for which a consistent supply of glucose and oxygen (both delivered via the blood) are required. Further, the delusional thinking present in schizophrenia could be explained by the putatively increased neural noise levels combined with a lack of mode two processing (inducing both erroneous results and the lack of the depth of reason necessary to debunk them) in schizophrenics. This possibility is supported by a study by Masicampo et. al. (2008), which found that blood glucose levels manipulated with lemonade alone could induce processing level differences (compared to a control group). It stands to reason that this would also apply to inconsistent oxygen supply (as would occur with improper ischemic vasodilation) in schizophrenics as oxygen is required for the cellular respiration necessary to utilize the glucose obtained from the blood.

In addition to explaining these more internal deficits, interactions with the larger environment can be explained using the proposed model as well. One example of such an interaction is that between schizophrenics and nicotine. Many studies have found that schizophrenics smoke significantly more packs per day than controls (e.g. Rupp et. al., 2005). This can be explained by the putative model plus two additional factors. The first of these factors is that schizophrenics tend to have impaired vasodilation response to nicotinic acid (formed in the blood after smoking tobacco). The second factor is that metabolites of nicotine, such as cotinine, cause vasodilation

to occur. These factors taken together suggest that schizophrenics, on average, would have to smoke more cigarettes to achieve the vasodilatory results of cigarette smoking. The proposed model provides the impetus to smoke in the first place: to achieve short term alleviation of the reduction in vasodilation in response to ischemic stimuli. Unfortunately, it is likely that long-term, this is maladaptive because the build-up of carbon monoxide and dioxide in the blood will create the very conditions that the patient attempted to alleviate in the first place (micro-ischemic events) by lowering the amount of oxygen in the blood. This effect should become more pronounced with higher pack-per-day loads. The above points make it apparent that there would be a positive feedback loop between smoking behavior and symptomology in schizophrenics. This possibility places even greater importance on controlling for the effects of smoking when studying schizophrenia.

In addition to both internal and behavioral traits of the disease, the proposed model can help account for the efficacy of several treatments for schizophrenia. One such treatment is Haloperidol, an antipsychotic medication for which there exists a wide variation in the time it takes to achieve clinical response (as defined by a 20% reduction in symptomology). Within this variation, it takes 8 weeks for 90% of patients to achieve clinical response. This suggests that long term compensatory changes mediate the efficacy of this drug (see below for details on this mechanism). Despite the large time delay in achieving efficacy, response to treatment within a single week is highly predictive of clinical response at 8 weeks. In fact, only 40% of those who had not responded after 1 week of treatment achieved clinical response after four weeks (Emsley et. al., 2006). This

suggests the contribution of more short term mechanisms to the efficacy of Haloperidol as well.

The short term actions of Haloperidol are consistent with the proposed model as Haloperidol is a D2 receptor antagonist (likewise, many antipsychotics are dopamine receptor antagonists). In the short term, Haloperidol would therefore have the effect of increasing the amount of synaptic dopamine by blocking the binding of dopamine to available receptors. Dopamine has been found to be able to induce microvascular vasodilation in the brain in an effect at least partially mediated by D1/D5 receptors. This is especially so in the striatum (Choi et. al., 2006). Thus, a dopamine receptor antagonist (like Haloperidol) should increase the vasodilatory effects of dopamine, which should prove to be neuroprotective. In schizophrenic males, this effect should be compounded by the fact that in one third of the male schizophrenic cohort Haloperidol causes an increase in oestrogen levels (Rossler & Hafner, 1993), thus helping to counteract the problem of a oestrogen mediated issue in nitric oxide induced vasodilation. This neuroprotection should occur by augmenting schizophrenics' poorly functioning nitric oxide mediated vasodilatory pathway, and thus increasing oxygen availability during potential ischemic events (i.e., helping to prevent ischemia from occurring).

The long term effects of Haloperidol are also consistent with the proposed model because Haloperidol has been shown to engender an average increase, compared to the age-corrected baseline values derived from the eight antipsychotic-naive control subjects, of 34% in the D2 binding potential (a combined measure of affinity for a receptor and receptor density) in a group

consisting of both novel and traditional antipsychotic patients (Silvestri et. al., 2000). This long term D2 receptor activity up-regulation may well provide the additional efficacy which causes many patients to achieve clinical response after several weeks of treatment. This is consistent with findings by O'Neil et. al. (1998) which suggest that increasing D2 activity is neuroprotective in rats (this is more fully discussed above). This neuroprotective effect should be further augmented since sensitivity of D2 receptors is negatively correlated with amount of oestrogen present (Hafner et. al., 1991). Because of this and the fact that schizophrenics tend to have reduced serum oestrogen (Rossler et. al. 1993), they should also exhibit increased dopamine receptor D2 sensitivity. The combination of this increased sensitivity to D2 activity and its up-regulation should be highly neuroprotective. This notion, in confluence with that in the preceding paragraph, demonstrate that the proposed model accounts for both the long term and short term efficacy of antipsychotics in providing protection against (short term) and mitigating the results of (long-term) oestrogen mediated micro-ischemic events in schizophrenics.

Haloperidol and other medications used to treat schizophrenics are also consistent with the model proposed in this paper because schizophrenics who are medicated display a drop in the amount of entropy in their resting electroencephalogram (EEG) compared to their pre-medication levels (Fernandez et. al., 2013). Entropy (when applied to EEG) measures the predictability of future EEG activity from previous activity, with increased entropy indicating a decrease in the predictive value of this previous activity. The predictive value of previous activity should, by definition, be

decreased by increases in the level of neural noise in the brain of the individual whose EEG is being recorded (thus increasing entropy levels). Because of this, entropy is an indirect measure of the levels of neural noise in the brain. Therefore, the decrease in entropy levels in medicated schizophrenics is consistent with the idea that mechanisms that induce neural noise increases in the brains of schizophrenics are causal in producing the disease's symptomology because medication decreases both neural noise levels and symptomology in schizophrenics.

The model proposed in this paper is also consistent with the treatment value of a more recent medication used in the treatment of schizophrenia, namely recombinant human Erythropoietin (EPO). EPO has been shown to improve cognitive symptoms of schizophrenia and attenuate progressive gray matter loss in schizophrenic men when a high dose was administered weekly (Ehrenreich et. al., 2010). This is consistent with the model proposed in this paper because EPO is widely used as a neuroprotective agent. Notably for the purposes of this paper, EPO was successfully used (by the same researchers) in the prevention of damage from ischemic stroke for several years before it was successfully tried as an adjunct treatment for schizophrenia. The treatment value of EPO in reducing ischemic stroke damage, loss of tissue (which could conceivably result from such damage) in schizophrenics, and the cognitive symptoms of schizophrenia establishes a further correlation between these reduced factors, which supports the proposed model's intertwining of them.

A final feature of schizophrenia that can be explained by this model is the course of the disease itself. One debate in the literature

has been whether schizophrenia is simply a neurodevelopmental disease or is a neurodegenerative one as well (Duncan et. al., 1999). The model proposed here reconciles many of the features of this debate in the following manner: in this model, during the initial prodromal period, symptoms are caused by the instability of blood oxygen flow to brain areas. This prodromal period is usually delayed in onset until adolescence for several reasons. The first of these is cerebral oxygen demand ($CMRO_2$) increases with age, peaking at 21-30 (Hafkenschiel et. al., 1953). This, incidentally, includes the range of age of onset most common for schizophrenia. Although this study was conducted in hypertensive patients, they provide extensive evidence showing that this group does not differ from normal in $CMRO_2$ levels (and additionally, as will be discussed later, hypertension occurs often in schizophrenia). The trend found in this study suggests that the putative deficits of oxygen supply to the brain present in schizophrenics are not severe enough to manifest until blood oxygen demand (and thus, to a certain degree, vulnerability to ischemia) increases. The late age of onset of the disease can also be explained with evidence from a mouse model suggesting a higher vulnerability of white matter to ischemic damage with increasing age (Baltan et. al., 2008). If this generalizes to humans, then this would also help to explain the later onset of the disease (because ischemia will be less detrimental earlier in life).

When the prodromal period does begin, little micro-infarct occurs as a result of the deficiencies present in schizophrenics because of the protective effects of brain-derived neurotrophic factor (BDNF). This allows for some progression of the disorder, but minimal overall effect compared to what is to come. At this point of dynamic

equilibrium, gross structural abnormalities are progressively accrued, increasing the patients' vulnerability to a causal stressor over time (hence the high age of formal onset of the disease). Such a stressor may upset this dynamic equilibrium as stress has been shown to decrease BDNF levels (Bremner, 1999). This effective reduction in the amount of BDNF protection afforded neurons would be compounded due to abnormalities in the expression of BDNF in schizophrenics reported by Asche et. al. (2001), such as reduced serum BDNF, reduced Messenger Ribonucleic Acid (mRNA) for BDNF, and an allele variant of BDNF in some patients. At this point, the formal onset of the disease may occur due to micro infarct (and increased effects of ischemia due to accrued structural abnormalities) in vulnerable areas. This relatively larger and more sudden accumulation of damage may account for the phenomenon of a "schizophrenic break" [to use a familiar analogy: this situation mirrors the action of neurons upon one another in engendering an action potential where structural changes accrue in the form of opening and closing ion channels, and eventually, given a 'causal' stressor, these changes will overcome the threshold for firing at the axon hillock, and an action potential will ensue]. The results of this break should vary according to the unique pattern of structural abnormalities accrued during the prodromal period and the resulting differing vulnerabilities to decreased reliability of blood oxygen in separate areas of the brain. These structural abnormalities, through their interaction with individual differences in both the stress of the disease itself (causing a further reduction in BDNF) and in the amount of BDNF suppression caused by this stress, should determine the chronic nature and the unique course of the disease in each individual.

After this schizophrenic break occurs, the degeneration generally peaks and symptoms begin to gradually lessen. The great capacity of humans to adapt to stressful situations can explain this phenomenon, as gradually the disease state becomes less stressful, and thus levels of BDNF may rebound. This process of symptom reduction may then be augmented by long term plasticity of the human brain, and by the fact that a relatively small number of new neurons are continuously generated in the adult brain (Johansson et. al., 1999). Both of these facts may lead to adaptations to the damage that has occurred, and thus a reduction in overall symptomology. The lack of progression of the disease after a certain point may also be attributed to the severity of the micro ischemia, which may not be severe enough to effect many areas of the brain. This would mean that after a period of degeneration, the disease would cease to progress as it would have effected all areas within this threshold. This model of the disease course is consistent with the findings of Asche et. al. (2001), which suggest that there is a role of BDNF in schizophrenia. Further, it is consistent with the well documented ability of stress to precipitate the onset of as well as relapses in schizophrenia. Finally, the micro ischemia model is also supported by findings that reduced chances of recovery occur, along with increased residual symptoms, after each relapse (Duncan et. al., 1999), as each relapse signifies a period of more rapid accrual of damage.

Now that the basic support for this model has been established, it is worth exploring several conclusions that follow from this model. One such logical sequel to the idea that the symptoms of schizophrenia are mediated by an oestrogen deficit resulting in vascular dysfunction is that the rates of coronary heart disease (CHD)

should be increased in patients over controls. Indeed, this is the case: a study by Cohn et. al. (2004) found that the ten year risk of myocardial infarction is higher in patients (both male and female, although only significant for the men) than in a control population. This risk increase cannot be explained by the increase in smoking rates alone, nor can it be explained by increases in total cholesterol levels. This suggests that something must be physiologically abnormal in schizophrenics' vascular systems, just as the model put forth here postulates. This is supported further by findings in many studies that there are region-specific reductions in blood flow in the brains of schizophrenics, and that these correlate with negative symptoms (c.f., Coyle, 2013). Interestingly, the schizophrenics studied by Cohn et. al. (all inpatients) had a two times higher risk for metabolic syndrome, which includes hypertension, compared to controls. The huge increase in the prevalence of this disorder in this population of people with the worst symptoms (those who are inpatients) among their cohort (schizophrenics) suggests that high blood pressure makes the symptoms of schizophrenia worse. This is consistent with the model of ischemia mediating schizophrenic symptoms, as high blood pressure and metabolic syndrome would put additional strain on an already stressed cardiovascular system.

Additional support for the idea that increases in blood pressure are detrimental to schizophrenics comes from the combination of the findings of two studies. The first finding is from a study by Robertson et. al. (1978), which showed that caffeine causes mean blood pressure to rise 14/10 mm of mercury one hour after caffeine ingestion in healthy controls (in short, caffeine can cause acute blood

pressure increases). This finding is augmented by that of Lucas et. al. (1988) which showed that 10mg/kg of caffeine administered to schizophrenics worsens several measures of the presence of psychosis and increases diastolic blood pressure in schizophrenics. These two finding's confluence is consistent with the idea that increased blood pressure can worsen schizophrenia symptoms, and thus provides additional evidence for micro-ischemic events as the proximate cause of schizophrenic symptoms. Further support for this (and thus the proposed model) comes from a recent study by Hallack et. al. (2013) which found that a single dose of nitroprusside caused a persistent (for 2 weeks after treatment) and rapid reduction in symptoms in schizophrenics (Coyle, 2013). Although these results are still being treated with caution due to the experimental design, this finding (if sound) is significant because nitroprusside is used clinically to reduce blood pressure in hypertensive individuals. In addition to its ability to cause a reduction in blood pressure, nitroprusside can cause vasodilation, thus increasing cerebral perfusion. This action of nitroprusside combined with its positive effect on schizophrenics is also consistent with the proposed model because it would allow for increased oxygen supply to the brain (and thus a reduction in ischemic events) while helping to ensure vasodilation when these events occur.

It is important to note that although the above points offer seem to offer a simple avenue to treat schizophrenia (namely, increasing NO levels with treatments such as nitroprusside), this should be done with caution for several reasons. The first of these reasons is that nitric oxide may activate the Hypothalamic-Pituitary-Adrenal (HPA) axis (Palsson et. al., 2010). This suggests that the increases in nitric oxide levels (which may

in the short term help to compensate for resistance to the chemical's vasodilatory effects) which occur in schizophrenics (Karson et. al., 1995) may actually be maladaptive long term because this increase may amplify stress responses. The second of these reasons is that nitric oxide is associated with the generation of neurotoxic reactive oxygen species. As mentioned above, these cautions may also apply to treatments targeting NMDA receptors since activation of these receptors leads to calmodulin mediated activation of nitric oxide synthase (Coyle, 2013).

A second consequence of vascular dysfunction in the brain is that similar pathology should be seen in the retinas of schizophrenic patients. This should occur because there is a large body of evidence (see Patton et. al., 2005 for a review) which indicates that the state of the microvasculature of the retina is indicative of that in the brain. There is currently a large amount of evidence for such retinal pathology in schizophrenics. For example, 82% of the 23 total chronic schizophrenic patients in a study by Smith et. al. (1997) had one or more gross ocular abnormalities. These abnormalities mirror gross structural changes in the brain, and would be expected if the vasculature of both systems mimicked each other (as has been shown) and if the cause of these changes in the brain was mediated by vasculatory system abnormalities (as proposed in this paper). When examining the fundus (the back of the eye, including the retina) specifically, 52% of schizophrenic patients examined displayed some abnormality, and 46% had vascular abnormalities in this region (Vannas et. al., 1961).

This pathology in the retina, is worth examining in depth because it provides (as Patton et. al., 2005, indicate) good evidence

for the possibility that micro-vascular abnormalities such as those proposed in this paper's model of schizophrenia can lead to the functional abnormalities observed in schizophrenics. This can be demonstrated by examining the work of Cotton et. al. (1940). In this study, there was a high degree of correlation between the clinical status of the schizophrenic patient and the capacity of the retinal vascular bed. More exactly, this correlation was that patients who did not improve or who deteriorated had a relatively (to the improving group) small retinal vascular bed in a high percentage of cases. In contrast, patients who improved or recovered had a significantly larger retinal vascular bed. Further, longer disease duration was significantly correlated with lower retinal vascular bed volume (this appears to be a marker of susceptibility, and is not a direct result of the disease). These volume-status relationships were strengthened after correcting for body volume. If this is mirrored in the brain, this is consistent with the proposed model (as lower vascularization density should increase vulnerability to ischemia by decreasing net blood flow to the brain with a given blood pressure). This particular study's data is especially valuable because these patients are medication naïve (the first neuroleptic, chlorpromazine, was initially marketed in the 1950s). In addition to these structural abnormalities, abnormal retinal function (paralleling the abnormal function of the brain) is shown in schizophrenics in the form of abnormal physiological measures such as electroretinography. Interestingly, the severity of these abnormalities correlates with the severity of clinical symptoms of schizophrenics (Balogh et. al., 2008), which is consistent with the proposed model because it shows that there is a relationship between vascular and functional abnormalities in the eyes of

schizophrenics which should be mirrored in their brains.

A second consequence of the idea that the symptoms of schizophrenia are mediated by a deficit of oestrogen is that there should be a decrease in high density lipoprotein (HDL) which accompanies the disorder. This idea follows from the finding of Bush (1996) that women taking oestrogen replacement therapy experience an increase in HDL levels. Thus, a decrease in this hormone should result in the opposite phenomenon: a decrease in the level of HDL. This concept is consistent with the finding that there is indeed a significant decrease in HDL among schizophrenics (Cohn et. al., 2004). This could further exacerbate the vascular problems underlying schizophrenia, as HDL is known to help prevent arterial disease such as atherosclerosis (Barter, 2005).

To examine a different subtype of sequelae, a logical sequel to the ischemia related model of schizophrenia put forth in this paper is that there should be an accompanying leakage of fluid into the extra cellular matrix due to a decrease in membrane integrity. Also, there should be a decrease in the total volume of brain tissue (due to both sub-optimal growth and possible cell death) in schizophrenics compared to controls. Evidence consistent with this phenomenon is found in the research of Andreasen et. al. (1994), who state that compared with the controls, schizophrenia patients had a smaller average volume of total brain tissue and a greater average volume of total and ventricular cerebrospinal fluid (CSF). It stands to reason that there should be increases in total fluid volume if fluid is leaking into the extra cellular matrix. A second corollary to the idea of ischemia or infarct in schizophrenia is that there should be evidence of cellular

atrophy. Such evidence was found by Oxenstierna et. al. (1984) in the cortex and vermis on computed tomography (CT) scans of schizophrenia patients' brains. A third logical sequel to the idea of increased vulnerability to ischemia and infarct is that there should be a decrease in life expectancy that cannot be accounted for by symptomologies associated with the psychosis itself (i.e., self-injury and accidental death). This is exactly what was found by Brown (1997). A final logical sequel to this idea is that there should be evidence of oxidative stress in the brains of schizophrenics caused by a decrease in the level of available oxygen (which would cause oxidation in chemical reactions requiring more oxygen than available). Such evidence has been found in certain studies of the brains of schizophrenics after their deaths (Coyle, 2013).

A final logical sequelae to the putative model of schizophrenia put forth here is that the organism afflicted with the traits which will eventually develop into schizophrenia should logically increase the chances of bleeding occurring when the organism is interfaced with another organism (i.e., during pregnancy). This should occur because of unstable vasculature as a result of improper vascular responses to reductions in oxygen. Such increases in the amount of bleeding during the pregnancy of the mothers of schizophrenics has been found by researchers such as Austin (2005). Neural damage resulting from such bleeding, on the whole, should be limited, however, due to such protective factors as the presence of fetal hemoglobin, which has increased oxygen carrying capacity compared to normal hemoglobin (and thus should help to reduce the probability of ischemic events occurring in the first place). This fetal hemoglobin should continue to protect significantly against damage due to the

impaired vasodilatory response in schizophrenics until the third month of life, when fetal hemoglobin levels reach normal adult ones (Metaxotou-Mavromati et. al., 1982).

Limitations and Apparent Inconsistencies

Due to the complex nature of the schizophrenic disease state, several apparent inconsistencies between the proposed model and the current literature on schizophrenia have been accrued thus far. The main inconsistency that must be reconciled is that, as this paper points out, NMDA receptor antagonists alone are not effective treatments for schizophrenia (although they may be effective as adjunct agents). This seems to provide evidence against the validity of the proposed model (as well as against several older models of schizophrenia) because NMDA receptor antagonists have been shown to reduce infarct volume in vivo (Wahlestedt et. al. 1993), and should, by themselves, thus reduce symptomology progression if this model is correct. However, NMDA receptor antagonists alone have a lack of treatment power in schizophrenia (although they are used effectively as accessory treatments). This lack of power can be explained by the fact that NMDA antagonists cause excitatory components of neural networks to become uninhibited, and this in turn can cause neuronal damage (Onley et. al., 1999). Because of this, the net amount of protection conferred by NMDA receptor antagonists may be limited relative to the efficacy needed to attenuate symptoms. A second apparent inconsistency which one may have noticed is that O'Neil et. al. (1998) found that dopamine antagonists (like Haloperidol) were not neuroprotective in rats. This seems a contradiction to the explanation of the protective effects of Haloperidol offered here. However, it is important to note that

the rats used in that study did not have dysfunctions of the nitric oxide mediated pathway for vasodilation. Thus, the O'Neil study shows that once ischemia has occurred, dopamine antagonists are not neuroprotective, however it does not comment (as the explanation of Haloperidol's effects does) on the ability of such agents to prevent ischemia in the first place.

A limitation of the proposed theory is that in addition to the HDL increases that have been shown in schizophrenics, one would expect low density lipoprotein (LDL) decreases (as is seen in women taking oestrogen replacement). This is not seen in the literature to the knowledge of the author. This is a limitation of the putative model, and perhaps future research will illuminate the mechanisms which prevent the expected LDL rise. A further limitation of the model proposed in this paper is if infarct or ischemia is occurring, then there may be evidence of abnormally high levels of blood or traces of blood in the brains of schizophrenics when examined. This has not been demonstrated in the literature thus far, and is a topic that should be examined more closely in future research. The lack of this demonstration thus far should not be taken as a large mark against the validity of the model due to the fact that under most of the current models being used there would be no reason to look for the presence of blood in the brains of schizophrenics. Because of this, many studies which may have found blood traces may have missed them. A final limitation of the proposed model is that it, for the purposes of simplicity in this paper, does not differentiate between the subtypes of chronic schizophrenia. This putative model may not be equally valid for each subtype, and thus generalization of findings against or in support of this model between subtypes should be treated with caution

when applying them to other subtypes of the disorder (e.g., familial schizophrenia vs. non-familial types).

Conclusion

In conclusion, several researchers have predicted that patients with schizophrenia "may be more susceptible to the neurophysiological perturbations of environmental experiences that occur in the context of daily life, as their compensatory capacity is compromised and more easily breached. If prolonged or recurrent, such perturbations can lead to a persistent state of dysregulation, and potentially enduring pathologic changes, which are at first functional and ultimately structural" (Duncan et. al., 1999). The model proposed in this paper conforms to these predictions beautifully, and, to the knowledge of the author, this putative mechanism has not been proposed prior to this article. The considerable (albeit circumstantial) support for this model (along with its surprising explanatory power) warrants further investigation.

Several possible routes for this investigation are suggested by the discussion in this paper. For example, one possible region to focus on in order to find this effect was inadvertently identified by Rupp et. al. (2005). In this study, a sub region of the hippocampus (the subiculum) was identified that is active only when discriminating between odors and not during other olfactory tasks including other olfactory memory tasks. This area seems like a likely candidate for damage in schizophrenia as it would explain the olfactory discrimination deficits present in the disorder that were discussed in this paper. Another possible route for further examination of the proposed model is that, one could test this model's prediction that schizophrenics

should become more vulnerable to the induction of neural noise over time (i.e., a prodromal stage schizophrenic less so than one who has had a chronic form for several years). This should occur because increases in the net amount of damage over time should amplify the underlying pathology of the dopamine system resulting in unstable neural representations of stimuli. A second possible experiment to explore this model's validity is that schizophrenics with higher hemoglobin oxygen carrying capacity should have increased ages of onset of the disorder and possibly decreased symptom severity and risk of developing psychosis (i.e., blood oxygen carrying capacity should be predictive of whether and how quickly the onset of schizophrenia occurs in clinical high risk individuals). This should occur because higher blood oxygen levels would help reduce the probability of ischemic events occurring in the first place.

By exploring this possible ultimate cause of schizophrenia through experiments such as these, new and more effective treatments and early diagnostic tools may be developed which improve our repertoire of methods that help to alleviate the immense suffering caused by this disease.

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