Are there alternatives to dopamine hypothesis in order to explain schizophrenia?

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Abstract
This paper discusses a number of answers to the question posed above in researchgate.net: https://www.researchgate.net/post/Are_there_alternatives_to_dopamine_hypothesis_in_order_to_explain_schizophrenia?. Hopefully the readers will find some clues for further investigation.

Introduction
Traditional models of schizophrenia have emphasized dopaminergic dysfunction. Over the last 20 years, however, Limitations of the dopamine model have become increasingly apparent, necessitating development of alternative models. One of these alternative models are glutamatergic models, proposed by Dr. Daniel C. Javitt. See his 2010 paper in http://doctoronly.co.il/wp-content/uploads/2011/12/2010_1_2.pdf.

Answers

1. Gavin Reynolds
I'm not sure if your question is a rhetorical one - you do seem to have answered it, in part at least. But the dopamine hypothesis really only provides an explanation for a partial mechanism of positive symptomatology and does not inform us about the neuronal pathology. You might like to look at the discussion from a while back: https://www.researchgate.net/post/What_is_the_current_status_of_the_dopamine_hypothesis_in_the_etiology_of_schizophrenia?ev=tp_feed_post_xview

2. Lubos Janu
In real world, in real patient we can not separate one monoamine. This is network of several neurotransmitters, (plastic) neuronal connection, influencing hormones etc. Dopamine hypothesis is the most simply hypothesis explaining effect of antipsychotics. This is easy to use as tool for educational activities. So, as simplification. Other simple hypothesis have less "applicability" But it is complex procedure and too find another simple hypothesis is not meaningful.

3. Ludmyla Kandratavicius
Here (http://www.ncbi.nlm.nih.gov/pubmed/23699763) there is a different approach to treating schizophrenia that corroborates the Glu/NMDA/NO hypothesis, although further studies are

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necessary.

4. Ulla Karilampi
The last ten years there has been an increased interest in the anatomical and functional networks of the brain. Studies have shown that these networks are unbalanced in schizophrenia, with too high activity in some areas and too low in others. This actually matches the dopamine hypothesis, even though no studies can be found on the eventual correlation between these.

For example, see http://www.ncbi.nlm.nih.gov/pubmed/22981811

5. Richard Fardig
There is also the "inflammation hypothesis", suggesting systemic inflammatory conditions in individuals with schizophrenia and first episode psychosis. To my knowledge, studies have so far been inconclusive whether this is of etiological relevance or if it reflects epiphenomena related to secondary complications (metabolic, stress, etc.).

For example: http://schizophreniabulletin.oxfordjournals.org/content/early/2013/09/25/schbul.sbt141.short

6. Gavin Reynolds
In response to your question, Victor, you might start by asking "hypothesis for what?" when you consider these various neurotransmitters implicated in schizophrenia. What the glutamate hypothesis does, and the closely related GABA hypothesis (my favourite for over 20 years!) does even better, is to provide an understanding of the real, if subtle, changes in the brain that occur in the disease, and link them to the symptoms - to positive symptoms via dopamine, more directly to negative and cognitive symptoms. Dopamine cannot really address much of that. It also provides a means of relating aetiology - genetic and environmental risk factors - to the neuronal and neurotransmitter pathology.

7. Keiko Ikemoto
There is D-cell hypothesis.
D-neuron, i.e. trace amine neuron, induced from NSC, is a clue for pathogenesis of schizophrenia. There are several articles of D-cell or D-neuron, as trace amine-producing cells, modulating monoamine functions.

8. Susan Bachus
There is a recent line of evidence showing cholinergic muscarinic receptor involvement in schizophrenia. Brian Dean and Elizabeth Scarr at University of Melbourne have published in this area

9. Hans Rasmussen
see recent PET studies by Rasmussen et al pointing to a role of serotonin 2A receptors: e.g.

Decreased frontal serotonin2A receptor binding in antipsychotic-naive patients with first-

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episode schizophrenia. Arch Gen Psychiatry 67:9-16


and numerous studies by H.Y Meltzer

10. Anand Gururajan
   There's a hypothesis for schizophrenia based on almost every single neurotransmitter and neurotrophin in the brain. Not to mention, the hypotheses that are being generated based on disrupted intracellular signaling processes. Pick, choose or even combine hypotheses depending on what you want to study.

11. Emma Perez-Costas
   Hello Victor, if you need an starting point to look at the different current hypothesis available for schizophrenia, you will find concise explanations of several of the hypothesis in the schizophrenia forum web page: http://www.schizophreniaforum.org/

   None of the current hypothesis can explain fully schizophrenia simply because schizophrenia encompasses an array of individuals that are diagnosed in the clinic in base of the presence of a "consensus" number of symptoms. Even though there are solid findings linking anomalies in neurotransmission (dopaminergic, gabaergic, glutamatergic...), none of these are present in every single individual diagnosed with this "consensus diagnosis" that we call schizophrenia. On the other hand, quite often these anomalies are present in several major neuropsychiatric disorders, so perhaps we should start by forgetting about the clinical diagnosis and sub-diagnosis and start to think in the molecular pathways of all the array of anomalies that have been found regardless of the specific psychiatric disorder. This is the direction that the National Institute of Mental Health has recently starting to propose and hopefully more and more researchers in the field of brain disorders will start following.
   If you are interested in the new guidelines proposed by NIMH as the "Research Domain Criteria Project (RDoC), you can find them here: http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml

12. Bence Racz
   I think schizophrenia is a disease that has a quite obscure etiology. Partly because individual candidate genes account for only a small fraction of SZ, leading to the suggestion that multigenetic pathways may be involved. Obviously, we cannot exclusively blame dopaminine for SZ. You may want to read our recent article, where we used an alternative hypothesis in order to understand the background of this complex neuropsychiatric disorder: http://www.ncbi.nlm.nih.gov/pubmed/23554489

13. Emma Perez-Costas
   You are right, I am proposing to forget about the clinical construct. Genome Wide Association Studies (GWAS) have shown quite strong evidence that clinically-diagnosed major

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neuropsychiatric disorders such as schizophrenia, bipolar disorder, and major depression are not associated with unique biological pathologies, but rather share many common genetic traits. That is why I believe that the new NIMH guidelines are a move in the right direction. They propose a framework that provides a starting point to analyze biological pathology underlying clinical phenomena that may be common across multiple disorders. I am actually proposing exactly to do that for dopamine pathologies associated with neuropsychiatric disorders in a new grant that should be right now reviewed, but due to the shutdown will have to wait....The second problem when we address anomalies in neurotransmitter systems is the unfortunate assumption that for example in the case of the dopaminergic mesodiencephalic system, all dopamine cells will present the same pathology, which does not make any sense taking into account that these cells have different developmental origins, modulators, respond differently to insult, and very importantly, they are specialized in providing dopamine to different brain regions with markedly different functions.

14. Emma Perez-Costas
well, the problem is that most of the major neuropsychiatric disorders are not related to a single specific imbalance. I will never dare to claim that schizophrenia (or bipolar disorder, major depression...etc) are caused by the imbalance of this or this other neurotransmitter only. The problem is that what is diagnosed in the clinic is a "consensus" not a "real disease" from a biological stand point. If you have diabetes, you are diagnosed with specific biological/molecular tests to define your disease. If you are diagnosed with schizophrenia, this comes from observation of your behavior and responses following a manual for diagnosis, in which you are "classified" as suffering this or that disorder based in a somewhat subjective observation of multiple traits or symptoms. To make it even more complicated, you do not have to present all the symptoms listed in the diagnosis manual for that disorder(e.g the DSM-IV), you need to have a certain number of symptoms for a certain arbitrary period of time, which may or may not coincide with the symptoms observed in another patient diagnosed also with schizophrenia.
Hope that this is helpful and Best wishes.

15. Emma Perez-Costas
that is what I think is still to be discovered.....as the things are right now, from the standpoint of a researcher studying the biological/molecular pathology we could simply consider several of these disorders as within the same "spectrum"....to give you an example, in my not-yet-reviewed grant (thanks to the NIH shutdown), we propose to study a specific anomaly in dopamine in postmortem brain samples from individuals that were diagnosed with schizophrenia, bipolar disorder and major depression, and we propose to study them first as a single group compared to brains from individuals without psychiatric or neurological symptoms (i. e. our control group). Afterwards, we also analyzed them separating them by their clinical diagnosis to see if the deficit correlates in any manner with a specific clinical diagnosis, or if is equality prevalent regardless of clinical diagnosis. However, as a neuroscientist, what I am really interested in finding out is 1) the mechanism that yields this deficit, 2) which are the subgroups of cells that are affected, thus, we could know how to find specific treatments. There is quite a bit of work done in rodents but the most interesting for human pathology is the work published a few years ago by Vernier and Puelles showing different dopaminergic cells subgroups within the SN region: (http://www.ncbi.nlm.nih.gov/pubmed/11086287), so we really

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need to pinpoint which subgroups of dopamine cells are affected, and which circuitry their projections/processes contribute to. Finally, I am interested in the prevalence of this deficit in people diagnosed with a "major psychiatric disorder". None of what I exposed above goes against to continue using in the clinic for management purposes the current diagnosis system...at least until it can be figure out the pathology behind the symptoms presented in the clinic....and I remark the symptoms...not the clinical diagnosis, because "schizophrenia" probably will not hold as a "disease" and will not be easily explained as a "whole". Sorry that I cannot be more specific but this is a yet-to be funded project :)

16. Anthony Gordon

" How does the dopamine hypothesis explain positive symptoms of psychosis rather than 'explaining' schizophrenia!"

I have postulated for a long time that auditory hallucinations, whether occurring in normals after drugs, in religious mystics, schizophrenics, persons with ear diseases, etc, etc, develop out of tinnitus, a disorder of the (hypersensitised) inner ear. The brain circuits for tinnitus are identical to dopamine brain circuits. See also this recent Science paper:

"Science 6 September 2013: Vol. 341 no. 6150 p. 1041
Deafness and Misbehavior
Behavioral problems accompanied by hyperactivity often occur in children with severe hearing loss and vestibular impairment. Explanations have focused on socioenvironmental factors, but Antoine et al. (p. 1120) found that inner ear defects can cause dysfunction in the striatum, which leads to abnormal behavior—especially hyperactivity—mediated by dopamine and glutamate signals, in an area of the striatum that is instrumental in controlling motor output. The abnormal behavior can be reversed by injection of an extracellular signal-regulated kinase inhibitor, which provides a novel target pathway for the treatment of behavioral disorders."

17. Christoph Metzner

Quite recently, also the GABAergic system has been associated with schizophrenia. For example:

18. Paul Dessauer

This paper from 2008 discusses the "dual state" theory of dopamine dysregulation;

There is a pretty sound review, written in Dec 2012, of the dopamine hypothesis here;
http://www.schizophreniaforum.org/for/curr/AbiDargham/

In regard to the many neurotransmitters and structures implicated in symptoms of schizophrenia, or the progression of the illness, this article (below) lists 20 potential targets for pharmacological treatment;

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21. Victor Christianto
   Dear Keith, I see that you have two publications related to schizophrenia. I have two additional questions:
   A. One psychiatrist that I know says that schizophrenia needs lifelong medication. Is it possible to stop medicine if the condition is getting better, and when?
   B. Is it possible to use natural medicine as treatment for schizophrenia? Are there articles supporting this natural treatment?
   If you can answer these questions, I will really appreciate. Thank you

22. Keith Ford
   There is a strong opinion that Schizophrenia should be treated with antipsychotic medication and that a person should be on this for life. There is also some evidence suggestive that relapse rates match non-compliance with medication too. But ... I have equally seen and heard from users of services with a diagnosis of schizophrenia that have recovered and no longer use medication. As with all aspects of schizophrenia there are individual factors so as far as an optimum time for reducing medication and stopping, for one person it may differ to another. I guess research has a tendency to value quantitative methodologies and pays less value to qualitative and narrative research which are more personal for individuals. It is this research approach that you would read more of recovery and managing medication free. I am not against medication, but I feel that other approaches can also be used such as talking therapies and empowering approaches. I have not heard of any effective herbal or natural treatments for schizophrenia but I am sure there will be some out there that people will advocate works for them.

23. Paul Dessauer
   Victor's question is; "Are there alternatives to dopamine hypothesis in order to explain schizophrenia?"
   Dysregulation of dopamine is quite clearly causally related to acute episodes of psychosis, but this is of an "explanation" for acute positive symptoms, not for schizophrenia itself.
   Some studies suggest the chronic negative symptoms of schizophrenia are also related to dysregulation of dopamine- and it is probably significant that while toxic doses of dopaminergic drugs like methamphetamine can provoke a psychotic episode in otherwise "healthy" people, the symptoms of withdrawal from a serious methamphetamine dependence closely resemble the negative symptoms of schizophrenia- (lack of energy/enthusiasm, social withdrawal, dysthemia and anhedonia, problems with concentration and memory, problems with mood control).
   However, once again, this does not explain WHY a person diagnosed with a psychotic disorder experiences high or low levels of dopamine at differing times or in different parts of the brain...

   The distinction Emma has drawn between the way physical illnesses are diagnosed (typically by identifying the discreet disease causing agent) as opposed to how mental disorders are diagnosed (by clusters of symptoms) is an extremely important one.
   I am increasingly of the opinion that there is no such thing as "true schizophrenia" at all (if by this we mean a discreet disease entity). All people have the potential to experience psychosis, (it is a phenotype, not a genotype), and also to experience the negative symptoms of schizophrenia, but vulnerability to experiencing these sorts of symptoms varies widely across the population.

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24. Paul Dessauer

Some people (due to a combination of co-occurring genetic risk factors, and/or infection, neurological insult, or injury in-utero or in early infancy, and/or certain types of life experiences—especially social dislocation and repeated social defeat) are far more prone to psychotic breaks, and some people are far more robust in this regard. Even the least vulnerable humans can experience psychotic states if you stress them enough, (prolonged sleep deprivation, malnutrition, dehydration, extreme fear or anxiety provoking environments, stimulant toxicity, etc).

25% of people who experience a “first episode psychosis” never experience a second episode. They don’t have a disorder. They have just had a bad experience that has triggered this sort of response.

Those people who are most vulnerable typically have a family history of psychotic disorders, and we know that a large part of your risk of being diagnosed is heavily influenced by heritable factors. There are many studies that clearly show an association between certain single nucleotide polymorphisms (SNiPs) and a diagnosis of psychotic disorders. However studies in different populations identify completely different SNiPs as significant risk factors. There are dozens of them. And none is a sufficient or necessary causal factor in and of itself.

http://snpedia.com/index.php/Schizophrenia

25. Paul Dessauer

I am becoming more and more convinced that this means there is no real, single disease entity we can call Schizophrenia. Instead, I am tending towards the opinion that the cluster of acute symptoms that identify stress-related psychotic breaks, drug-induced psychosis, Schizophrenia, Schizophreniform disorders and Bi-Polar Affective Disorder are simply a phenotype that humans may express in response to stressors in their physical and social environment, but that the likelihood of any experience triggering this response in any individual is heavily modulated by genetics and experience in-utero, perinataly, in early childhood, and (perhaps to a less significant extent) by later life experience.

Those people with many co-occurring risk factors, who experience psychosis chronically, will typically get diagnosed with a form of Schizophrenia or a form of Bi-Polar Disorder. Studies into the heritability of both disorders identify the same familial risk factors, and the same factors are also associated with Autism.

<<< The first diagnostically unrestricted twin study using blinded diagnostic assessments concluded that the genetic vulnerabilities to schizophrenia and to mania were more overlapping than distinct: strong genetic components were found for schizophrenia (82%) and mania (87%); diagnosis-specific genetic variance accounted for 33% (schizophrenia) and 19% (mania) of variances; common genetic variance shared by both diagnoses accounted for 49% (schizophrenia) and 68% (mania) of variances. >>>


This is consistent with the idea that these diagnostic labels are not describing distinct disorders,

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but instead are describing different expressions of a wide spectrum of potential human behaviour.

"it is tenable that these disorders are more similar phenotypically than currently appreciated, and it might prove interesting to re-evaluate the degrees of demarcation between these three disorders,"


http://www.medpagetoday.com/Pediatrics/Autism/33589

http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=3405404

http://journals.cambridge.org/production/action/cjoGetFulltext?fulltextid=1936780


http://schizophreniabulletin.oxfordjournals.org/content/38/3/475.short

26. Shivraj Vhanale
In schizophrenia currently glutamate hypothesis and gaba hypothesis are important.

27. Anthony Gordon
"In schizophrenia currently glutamate hypothesis and gaba hypothesis are important"

Possibly, but this should not detract from the fact that the dopamine story is the single most significant contribution of neuroscience to schizophrenia. And there may not be any contradiction between these rival theories. Note this extract from Science (see post from yesterday:
"ear defects can cause dysfunction in the striatum, which leads to abnormal behavior—especially hyperactivity—mediated by dopamine and glutamate".

28. Anthony Gordon
"these "disorders" could be seen as a gradient or a spectrum, but not as separated entities"

I think it is more complicated than that, and I don't think I have quite sorted it out in my own mind. However, it is surely not analagous to the normal dimensional paradigm, eg blood pressure, with normality at one end and pressure gradually increasing until at some arbitrary point it is convenient to designate a category of hypertension. This model might indeed apply to schizotypical traits, where one goes smoothly from normality through schizotypy to schizophrenia, but surely mania does not fit into this particular dimension?

29. Felipe Gomes
In my opinion these theories are not rivals. Schizophrenia should be explain based on a multiple neurotransmitter hypotheses. For example, several evidence have indicate that an NMDA receptor dysfunction and an impairment of PV(+)-interneurons in schizophrenia could result in anomalies in dopaminergic neurotransmission.

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30. Victor Christianto
Thank you Shivraj, Dr. Anthony Gordon, Felipe and Emma, for your answers. Aside of dopamine and glutamate hypothesis, perhaps social isolation may also induce schizophrenia, at least according to a report in 2010. See [http://www.sharecare.com/health/schizophrenia/social-isolation-increase-risk-schizophrenia](http://www.sharecare.com/health/schizophrenia/social-isolation-increase-risk-schizophrenia)

31. Anthony Gordon
"perhaps social isolation may also induce schizophrenia"

This was linked to a study noting more schizophrenia in urban areas. I think the explanation for this is far more likely to be due to excessive noise exposure, or more infection in infancy, than to social isolation. On the farming program on BBC Radio 4 this morning it was reported that farmers are making great use of Twitter to combat social isolation.

32. Felipe Gomes
There is a nice review published in Nature about environmental factors and schizophrenia.

Concluding remarks
Based on these discussions, among the researchers apparently the most important hypotheses to explain schizophrenia are dopaminergic and glutamatergic hypothesis. However, there are other hypotheses such as D-cell. Meanwhile, Emma Perez-Costas argue in favor of similar factors behind a number of disorders. Other possible factors are perhaps social-environment. All of these seem to need work.

Acknowledgement
Special thanks to all contributors who have shared their opinions to the question I asked above. Hopefully this short summary article will help you move forward.

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