



SCHIZOPHRENIA: A PATHOLOGICAL AND THERAPEUTIC REVIEW

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Abstract:

Schizophrenia is blatantly the most dreadful psychotic disorder we need to pry in, given its prototype symptoms, complex etiology, pathophysiology and treatment approaches. Furthermore, people in prime of their lives fall target to schizophrenia. This study reveals the general description and discusses diverse modes of the disease. The study advances with more focus on the mechanistic pathways and not only the conventional Neurotransmitter/Receptor theories, rather on newer neurodevelopmental approaches such as genetic susceptibility i.e. NRG-1 and DISC-1 and its associate biomolecules FES-1, NUDEL & LIS-1 standing, reelin association, DNA Methylation, calcineurin hypothesis, prenatal and perinatal manifestations & viral infections. Further this article encompasses classification of the clinical symptoms into positive, negative and cognitive deficit symptoms followed by the therapy for a clinically diagnosed schizophrenic patient and discussion of common paradox of FGAs and SGAs, considering the better efficacy with lesser EPS. It concludes with the brief discussion on need of compliance for the schizophrenic patients and how SGA Depot Injections are helpful for patients with poor compliance.

Keywords: Schizophrenia, DISC-1, NRG-1, CN, Reelin, SGAs, FGAs, EPS.

INTRODUCTION

Schizophrenia is blatantly the most dreadful psychotic disorder we need to pry in, given its

prototype symptoms, complex etiology, pathophysiology and treatment approaches. Furthermore, people in prime of their lives fall target to schizophrenia. At any given time 1% of the population globally suffers from this disorder sparing no race, age, gender or different geographical regions. Despite the relative lesser prevalence weighed against other life threatening diseases, the intense manifestation appearing in schizophrenic

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patients leaves them utterly disabled to perform daily activities resulting in psychological aggravation.

The extreme and ominous symptoms of this disorder lead to 10% suicide cases of the affected patients. Schizophrenia is identified as a neurodevelopmental disorder portrayed by massive disruption of mood, cognitive system and poor filtration of stimuli resulting in a severe paradigm shift.

Schizophrenia within itself may occur in diverse modes, such as

- **Hebephrenic/disorganized schizophrenia:** marked by incoherent & incongruous behaviour.
- **Catatonic schizophrenia:** when a patient exhibits a marked psychomotor disturbance causing excitement or stupor.
- **Paranoid Schizophrenia:** marked by delusions and hallucinations, often vocal and leading the patient astray.
- **Residual Schizophrenia:** patients who have had one episode justifying the building schizophrenia.
- **Undifferentiated Schizophrenia:** where evidence is not enough to point diagnosis in a certain direction and differential diagnosis is crucial.

Pharmacodynamic effects of LSD may explain the apparent symptoms of schizophrenia, almost certainly explained by its tendency to dislodge 5-HT from brain which is known to passively inhibit the hallucinations also explaining the lucid nature of REM dream state where 5-HT is inhibited. LSD25 contains an indole ring similar to 5-Hydroxytryptamine responsible for its 5-HT antagonist action. For the reason of these properties, such hallucinogens are used as model drugs to set off schizophrenia. Latent inhibition in animals is induced by MDMA and LSD which is reversed by APs.

Other than contemporary Neurotransmitter/receptor theories suggesting dysregulation of Dopamine, Glutamate and 5-HT, newer studies suggest the down-regulated transcription of protein "Reelin" might play a crucial role in pathology along with involvement of a group of potential candidate genes such as Neuregulin-1(NRG1), Distorted in Schizophrenia-1 (DISC1), COMT, Brain

Derived Neurotrophic Factor (BDNF) and dopaminergic pathway gene, involvement of Calcineurin (CN), Interleukins-8 (IL8), maternal TNF- α and prenatal viral infections which we shall discuss later in the article. Simply put, neurodevelopmental, prenatal and perinatal infections and manifestations lay a sovereign foundation of schizophrenic abnormalities.

PROGRESSION OF DISEASE & MECHANISTIC PATHWAYS

Schizophrenia exhibits strong genetic predisposition and heritability estimate ranging from 70% to 90%. Monozygotic twin of a Schizophrenic patient has concordance of 52 percent to be affected by the disorder. One thing is certain that schizophrenic factor is not limited to one gene. Chromosomes 6,8,13 and 22 are believed to have potential gene responsible for the disease. Cannabis/LSD/MDMA abuse has been found to be significant in etiology of Schizophrenia.

Attributing to environmental factors, Positron Emission Tomography has shown lower glucose levels and insufficient blood supply to frontal and left temporal lobe of the brain in schizophrenic patients.

Many schizophrenic patients show early onset of REM sleep explained by activation of dopamine release primarily in Substantia Nigra, secondarily in Ventral Tegmental Nuclei and Zona Compacta accounting to cholinergic activation in the neurons of Pedunculopontine and Laterodorsal Tegmental Nuclei. Patients with these manifestation show severe positive symptoms.

✓ Prenatal & Perinatal Viral Infections and Calcineurin Hypothesis

Studies have shown schizophrenia to be a neurodevelopmental disorder, environmental factors leading to cortical asymmetry i.e. enlargement of cerebral ventricles in left temporal horn in early prenatal months attributing it to maternal viral infections. If we are to discuss a few of these viral infections Rubella and Influenza would top the list. In a study, 20% of subjects off rubella exposed mothers were found to be schizophrenic indicating twentyfold increase

of risk. Similarly Influenza exposure presented seven fold increased risk. Maternal Immune Activation (MIA) plays the key role in susceptibility to the disease, maternal cytokine introduction to the developing foetus result in premature death of differentiating cells resulting in inappropriate development of neuronal system and consequent behavioural anomalies. These manifestations can be explained by association of elevated secretion of maternal cytokines, TNF- α , IL-8 and other pro-inflammatory cytokines in response to the viral infections with increased risk of schizophrenia. In a study conducted by Alan S. Brown, Columbia University, comparing to the control population, maternal IL-8 level were found to be twice as high during second-trimester of pregnancy for the offspring who would later develop Schizophrenia while lesser predisposition to maternal TNF- α was deduced, nevertheless posing the equivalent vulnerability to the disease (Figure 1.1).

Calcineurin (CN) otherwise known as protein phosphatase-3 works by inducing and activating Nuclear Factor of Activated T-cells (NFATs) which is vital for transcription of IL-2 genes. Adjuvantly Calcineurin catalytic γ -subunit plays an essential role in transcription of genes EGR-1, EGR-2, EGR-3 (Early Growth Response) which have shown striking association with schizophrenia. EGR is directly linked to neuregulin, dopamine & glutamate signalling and NDMAR expression. In a study, several Schizophrenic subjects were found to exhibit down-regulated EGR transcription in frontal lobe resulting from CN deficiency.

✓ **Reelin Hypothesis and DNA**

Methylation

Down-regulation or mutations of reelin transcription has been noted in schizophrenic patients. Reelin being a protein that assist regulation processes of neuronal positioning and migration of the developing brain in a foetus has been found in very low concentration in schizophrenic patients.

Reelin, a serine protease plays a crucial role in neurodevelopment explained by its (in)direct impact on B-catenin responsible for apoptosis, Tau, a microtubule-associated

protein vital for cell division found abundantly in brain and Glycogen Synthase Kinase (GSK-3B) responsible for cell proliferation. Cortical GABAergic cells and Cajal-Retzius cells are known to secrete Reelin glycoprotein. Reelin enters a neuron by binding to its receptors VLDLR, α 3B1-Integrin and ApoER2. Receptor clustering results in tyrosine phosphorylation of protein Dab-1, which sets in a positive-feedback loop resulting in termination of reelin signalling cascade, pDab-1 thus obtained directly causes synaptic plasticity and polymerises GSK-3B which further phosphorylates B-catenin and Tau to p-B-catenin and ptau respectively. Post-mortem studies of schizophrenic brain revealed DNA methylation changes specifically regarding Reelin gene. As a result of DNA methylation, reelin promoter gene is silenced and reversed by demethylation.

Schizophrenic symptoms progress throughout the patient's life. Misplaced cortical neurons amounting to early aberration of brain development rather than degeneration of cortex over a period of time may yet again point out the significance of reelin transcription down regulation or prenatal infections. A number of investigators established the facts of epigenetic dysfunction in schizophrenic patients viz. difference in methylation of cytosine pyrimidine (CpG) sites in genes for the D2R2 receptors and Catechol-o-methyl-transferase (enzyme responsible for catecholamine depletion) hampers the gene expression. Also deduced increased levels of DNA methyltransferase-1 (DNMT-1) have been associated with changes in the Glutamic Acid Decarboxylase67 (GAD67). Interestingly, it was found out that neither the duration nor the onset time of illness had altered the levels of either of the mentioned biomolecules in a group of patients with different duration and time of onset, which seemingly questions the very foundation of otherwise widely accepted view of epigenetic influences on disease chronicity.

Thus, the theory of DNA methylation needs reconsideration as mechanistic cause as some scientists believe these epigenetic dysfunctions may not be the cause of the disorder rather a consequence.

✓ **Genetic Susceptibility - NRG-1 and DISC-1 standing**

Of chromosomes 6,8,13 & 22, till date almost 9 genes are deduced to have schizophrenic factors relating to monoamine transmission and glutamate-mediated transmission (NMDAR expression). Genetic studies point none amine neurotransmitter like dopamine can be directly connected to underlying factors of schizophrenic abnormality. In an analysis Using Denaturing Gradient Gel Electrophoresis, no structural coding abnormalities in the dopamine D2 receptor (DRD2) gene were found to be present in schizophrenia ruling out Dopaminergic pathway gene polymerisation of DRD2.

NRG-1 gene works in close similarity to Reelin i.e. neuronal migration. NRG-1 encodes the neuregulin expression on its receptor erbB3. In several studies defected expression of erbB3 was detected in prefrontal lobe of foetuses leading to flawed neuronal migration and myelination and would later develop schizophrenia connecting NRG-1 gene directly in accordance with pathophysiology of the disorder.

DISC-1 first identified in a large Scottish family is a 414.3kb gene containing 13 exons and detected on chromosomal region 1q42.2. Its key manifestation is believed to be disruption of cellular cAMP signalling which has been directly linked to memory, learning and mood orientations through its interactions with Phosphodiesterase-4B. DISC-1 induces single nucleotide polymorphism causing mutations. Its associate molecules, Lissencephaly-1 (LIS-1), Fasciculation and Elongation Protein Zeta-1 (FES-1) and Nuclear Distribution Element-like (NUDEL) play a critical role in pathophysiology of Schizophrenia. In a study of schizophrenic brain, no difference in mRNA expression of DISC-1 was found but DISC-1 polymorphism and subsequent muffled expression of FES-1, LIS-1 and NUDEL were observed. In another study conducted by same cohort of scientists to deduce role of DISC-1 in developing brain, detection of DISC-1 in developing embryo of mouse from embryonic day 10 was done. Results showed positive response of DISC-1 expression on embryonic day 13 and postnatal

day 35 corresponding to neurogenesis and puberty pointing out the role of DISC-1 in neurodevelopment (Figure 1.2).

In other studies NUDEL was directly connected to play role in neuronal migration, neurofilament assembly and cytoplasmic dynein movement while LIS-1 is believed to play a role in regulation of corticogenesis. NUDEL is also known to slice several neuropeptides like neurotensin (NT). NT depletion by NUDEL assisted slicing are found active in schizophrenic patients, reversed by NT receptor antagonists causing increase in local concentration of NT and NUDEL inhibition and proves to be a strong candidate for antipsychotic action.

Insufficient axonal and dendritic communications lead to lesser neuronal connectivity and hence disturb the CNS homeostasis. Neurochemistry has had a little success in pointing out a marked chemical dysfunction in schizophrenic patients rather the accidental formulation and therapy of APs on schizophrenic patients and acquired results have helped deduce the apparent chemical dysfunctions in the brain.

✓ **Neurotransmitter/Receptor Theories**

Contemporary hypotheses and theories of pathophysiology in Schizophrenia evolve from pharmacokinetics & pharmacodynamics of psychotropic agents; we might arbitrarily call it reverse pathophysiology as opposed to conventional progressive pathophysiology. We are on large relying upon the results attained by therapies. Detailed studies of brain imaging of recently diagnosed patients and patients under Antipsychotic therapy gave birth to widely accepted theories relating to NTs dysfunction such as dopamine, glutamate and serotonin.

- **Dopamine Theory:** Proposed by Carlson. He observed Amphetamine users exhibit Schizophrenic behaviour pattern under the influence, accounting to large amount of dopamine release. These behaviour patterns were also observed in conditions of apomorphine (dopamine receptor agonist) dependency. Reserpine blocks the dopamine storage and effectively reverses the symptoms. But contrary to these findings there is no

evidence pointing out the excessive release of dopamine. Given the normal quantities of prolactin in patients, which otherwise should have been low responding to excessive dopamine. Within these controversies Laruelle in 1999 studied imaging of raclopride (D2 antagonist) binding in striatum and upon the injection of amphetamine the binding of raclopride was reversed accounting to excess release of dopamine and most interestingly, schizophrenic patients showed double fold response to amphetamine injection i.e. double fold release of dopamine. Another theory states that because of dopamine imbalance in brain, excessive D2 activation in mesocaudate region results in positive effects and hypofunction in cortical region results in negative effects.

- **Glutamate Theory:** Glutamate is an excitatory NT. Inhibition of NMDAR shows building schizophrenic symptoms as seen in dizocilpine and ketamine (NMDAR antagonists) induced psychotic symptoms. Post mortem studies of schizophrenic brain show less concentrations of glutamate and reduced receptors. Another study of transgenic mice having reduced NMDAR expression exhibit signs of social withdrawal, relating to negative effects of schizophrenia. Also reduced function of NMDAR shows cognitive deficit as observed yet again in negative symptomatic Schizophrenia. Hence it could be deduced that excessive release of dopamine or activation of D2 receptors amount to positive symptoms and decreased NMDAR activity amounts to negative symptoms.
- **5-HT:** Comparatively a vague theory, suggests that serotonin receptors might play a certain role in pathophysiology of schizophrenia, given the schizophreia like effects of LSD. Many APs prescribed for Schizophrenia have 5-HT antagonist pathway which conflicts with mechanism of LSD induced Schizophrenia, considering LSD also dislodges 5-HT but induces schizophrenia like symptoms and not exhibit antipsychotic property. The

credibility of this theory has yet not been established.

CLINICAL PRESENTATION

Unlike a laymen's knowledge of schizophrenia, it is not stereotyped as split personality disorder, rather it is a complex disease which affects the thought processing, so different individuals at registration of the same stimuli might arise different thought process, it is more dependent on the characteristic individuality of the patient. So far, is it fair to label it as multi personality disorder? We don't know yet.

More recently Cognitive Deficit, earlier a part of negative symptoms (as both being related to prefrontal lobe dysfunction) has now been studied in details and has now classified separately from negative symptoms. Positive symptoms are associated with temporolimbic abnormalities.

This separation still is unjustifiable given that poor or no education may build up cognitive dysfunction. And it is complex to compare and attribute universal symptoms of schizophrenic patients considering the different upbringing they went through.

Still based on latest approach to classify symptoms, three different classes have been established namely Positive Symptoms, Negative Symptoms and Cognitive Deficit.

- **Positive Symptoms:** seemingly observed in most of younger patients characterized by Suspiciousness/paranoia Delusions Hallucinations (nature varying as per individual character, voices are more common) Conceptual disorganization Catatonic conditions
- **Negative Symptoms:** observed in older patients exhibiting Refrain from social contact Anhedonia (inability to express pleasure) Flattening of emotions Avolition(lack of motivation) Alogia(fail to write or speak a language) Disorganized speech (attributing to impaired thought process) Ambivalence
- **Cognitive Deficit:** Impaired executive skills Impaired functional processing memory Impaired attention Impaired innate instincts Inability to differentiate between significant and insignificant stimuli such

as ticking of a clock might get the attention which an average unaffected person would overlook.

THERAPY

Post the hospitalization, depending upon patient's behaviour disorganisation, Antipsychotic medication is the treatment of choice. Relapse rate is almost reduced to half by APs therapy. To improve compliance and patients disregarding oral medications, long acting injectables may be preferred. Negative symptoms respond best to Clozapine(D4 blocker) having 1:1 chlorpromazine ratio while positive symptoms to depot injections. Adjuvant Antidepressants might be prescribed with Antipsychotics in case of building depression. BZDs are favoured in conjunction with APs for patients with severe catatonic conditions, lorazepam(2 mg orally) has been found to rapidly resolve catatonic conditions plus concomitant BZDs therapy has proved to be useful in dose reduction of an oral or parenteral AP. Risperidone (5-HT₂ & D₂ blocker) is favoured because of its still lesser EPS than haloperidol and does not require weekly monitoring like haloperidol and clozapine resulting in lesser cost of treatment. Though haloperidol given 10mg/day i.m. is readily absorbed and attains tenfold plasma levels than oral doses controlling to a greater level, racing thoughts and psychomotor agitation. Particular care must be taken while injecting haloperidol intravenously in critical cases with the intention to reduce the risks of cardiovascular side effects. Chlorpromazine like APs are most favoured given lesser EPS such as akathisia but opposing the inclination to induce lesser EPS, chlorpromazine like APs exhibit more anticholinergic and adrenergic side effects.

Medication for patients with one episode of schizophrenia should be narrowed gradually after about six months of therapy and clinical features should be maintained carefully, such patients have slim chances of relapse than patients with multiple episodes.

In the sphere of APs therapy, comes the perplexity to carefully choose the drugs of choice from conventional first Generation Antipsychotics and relatively newer Second

Generation Antipsychotics. Although there is not concrete touchstone to tell apart FGAs from SGAs, but the primary aim remains to obtain higher efficacy with no or very minimal EPS. According to widely accepted conception, FGAs exhibit more EPS shown by acute and chronic movement disorders

Considering D₂ receptor antagonists, receptor imaging showed that at D₂ receptor occupancy more than 75% is obligatory for the antipsychotic to exhibit its effects

Depot APs(long acting APs) which are generally

SGAs: Risperidone & Olanzapine pamoate long acting injection (once in four weeks) demonstrates effective and safety profile that of oral doses, but causes "post injection syndrome" such as hyperprolactinaemia and radical increase in body weight thus recent research still focuses on controlling these contraindications given injection effectively control the symptoms. Paliperidone palmitate is also under studies and possesses potential effects similar to both Risperidone & Olanzapine pamoate.

But there is a confusion surrounding the credibility of long acting injections owing to the complicated pharmacokinetics such as dose calculation and change in plasma drug concentration without change in dose attributable to its delayed release.

In another study to observe the trend of therapies, no significant differences were found in incidences or modifications of rating scales for Schizophrenic symptom such as dystonia, akathisia or tardive dyskinesia whilst comparing SGAs with perphenazine or comparing within the drugs classified under second-generation antipsychotics.

Secondary analyses gave away greater rates of concurrent antipsychotic medication among patients on risperidone therapy and lower rates among patients on quetiapine therapy. Lower rate of discontinuation contraindications were observed among patients on quetiapine and ziprasidone. There was a trend for a greater likelihood of concurrent medication for akathisia among individuals on risperidone and perphenazine.

COMPLIANCE

It is vital to evaluate the strategies employed to recuperate patient compliance with antipsychotic medication, given its obvious magnitude in therapy. Successful treatment for Schizophrenic patients necessitates the acknowledgment that poor compliance most certainly will present a major hindrance in achieving most favourable results. In such dire conditions depot injectables are the most judicious choice.

Decaonate form of fluphenazine and haloperidol dose varying from 12.5 mg to 100mg are long lasting with fewer EPS when given i.m. or deep s.c., the effect lasts up to seven days or a month. Consequently the patient with poor compliance will agree to visit a physician for these “shots”.

CONCLUSION

Given the complicated characteristics of Schizophrenia, differential diagnosis and careful therapy monitoring becomes very important. For further developmental research, prospective pathophysiological and epidemiology approaches are needed in the most promising sector of Genetics. Biotechnology might prove utterly useful in both pathophysiology and drug design for the Schizophrenic patients. Epigenetic approaches such as DNA Methylation need reconsideration as discussed earlier, since it might be the symptom and not the cause. More theories explaining the late onset of disease although predisposed in prenatal stages needed be postulated. Brilliant idea of tailored APs, designed for a particular patient through his/her genetic map need to be employed in a newer economic way.

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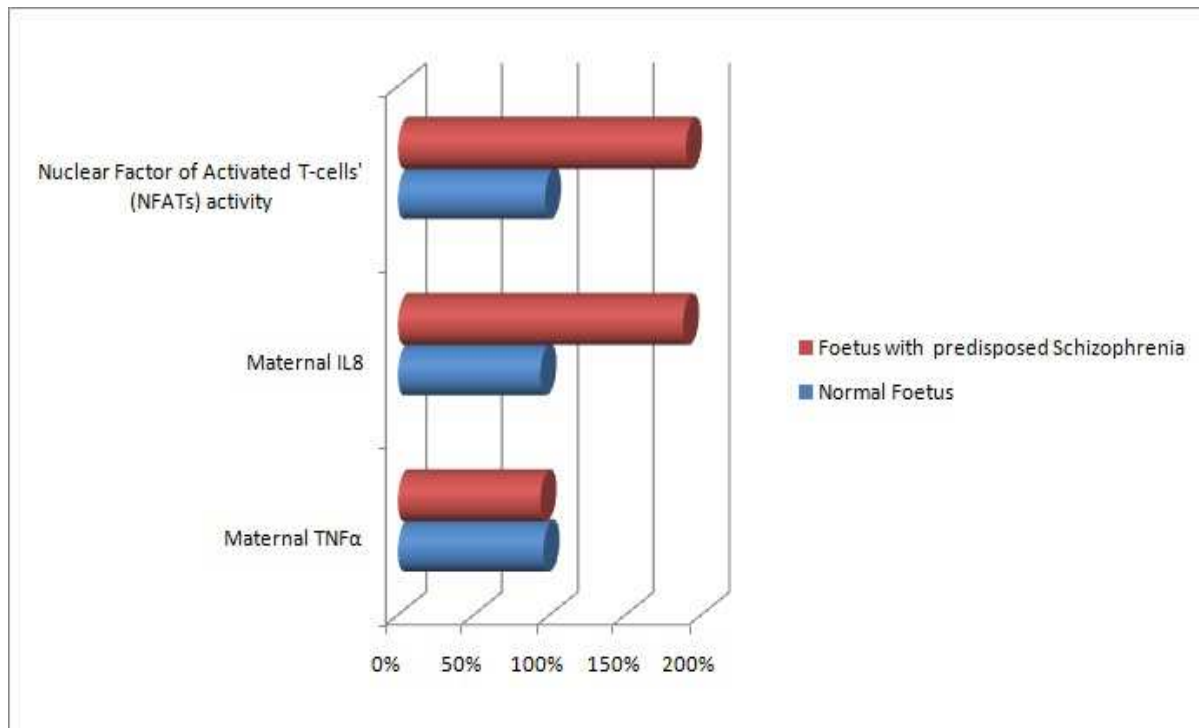


Figure 1.1: Maternal IL8, TNF Nuclear Factor of Activated T-cells' (NFATs) activity in a healthy foetus (100%) and foetus with predisposed Schizophrenia.

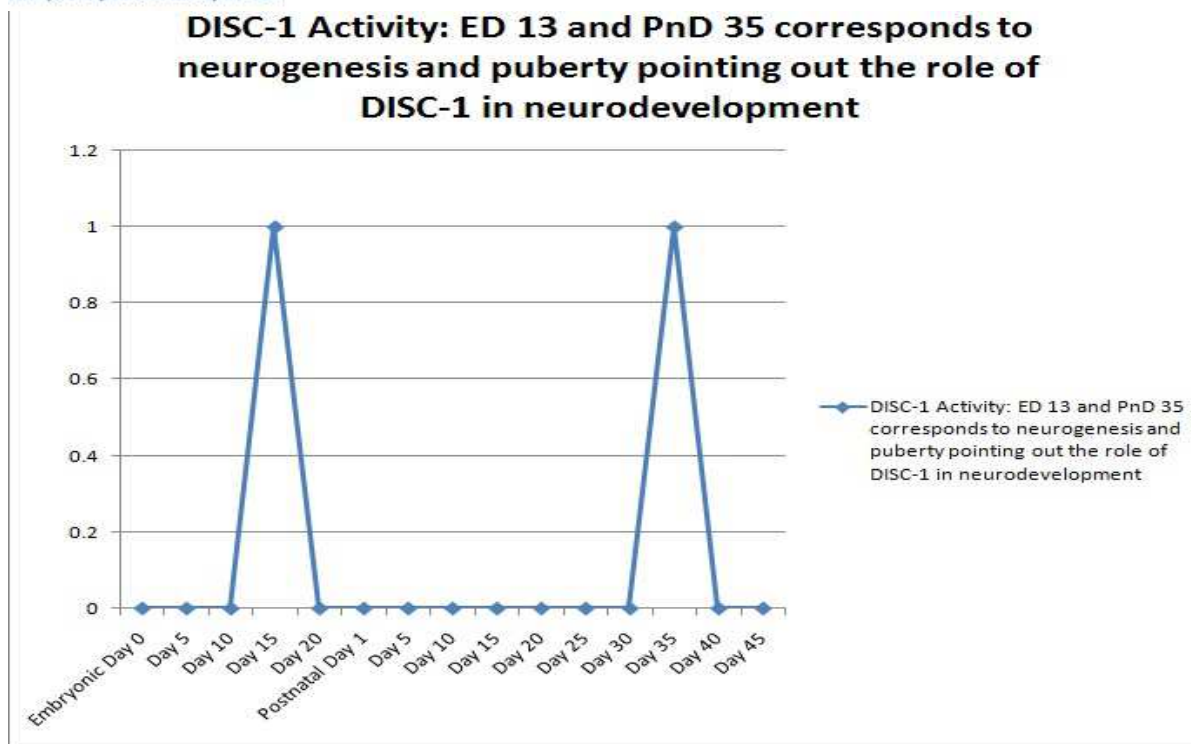


Figure 1.2: Peak DISC-1 activity observed in rodents on Embryonic Day 13 and Postnatal Day 35 corresponds to neurogenesis and puberty, pointing out the role of gene DISC-1 in neurodevelopment