**Summary**

Mental illness can arise from over-compensation of neural processes when they attempt to correct nervous system perturbation, regardless of the original cause. Initial brain compromise can be caused by genes, toxins, chemicals, infective agents, hypoxia or trauma. The original insult leads to a compensatory process of ‘rendering the synapse supersensitive’, a general neural mechanism that is involved in nervous system adaptation, repair, and regeneration. For example, in psychoses, the many and diverse early risk factors that underlie the psychosis converge to increase the number of supersensitive dopamine D2 receptors (i.e., D2 receptors that are in the high-affinity state for dopamine (that is, D2High receptors)).

The increase in D2High receptors may underlie behavioral supersensitivity, including the positive and negative signs and symptoms of psychosis, such as hallucinations, paranoia, mood swings and social withdrawal.

The forthcoming arrival of ‘fast-off-D2’ antipsychotic drugs should significantly improve treatment of psychosis by transiently occupying the D2 receptors, thereby minimizing unwanted side effects.

**Practice points**

- Dopamine D2 receptors are the main targets for antipsychotic clinical action.
- Various injuries, street drugs, or gene mutations can result in dopamine supersensitivity in a range of synapses in the brain.
- Although injury, street drugs, or mutations have little effect on the total number of D2 receptors, they cause a marked increase in the number of D2 receptors that are in the high-affinity state for dopamine (that is, D2High receptors).
- The increase in D2High receptors may underlie behavioral supersensitivity, including the positive and negative signs and symptoms of psychosis, such as hallucinations, paranoia, mood swings and social withdrawal.
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**Schizophrenia and the supersensitive synapse**

Philip Seeman† & Mary V Seeman†

**PERSPECTIVE**

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**SUMMARY**

Mental illness can arise from over-compensation of neural processes when they attempt to correct nervous system perturbation, regardless of the original cause. Initial brain compromise can be caused by genes, toxins, chemicals, infective agents, hypoxia or trauma. The original insult leads to a compensatory process of ‘rendering the synapse supersensitive’, a general neural mechanism that is involved in nervous system adaptation, repair, and regeneration. For example, in psychoses, the many and diverse early risk factors that underlie the psychosis converge to increase the number of supersensitive dopamine D2 receptors (i.e., D2 receptors that are in the high-affinity state for dopamine). Supersensitivity of synapses compensates for and protects the brain from further injury. This leads to heightened neurotransmission, which is experienced subjectively as overstimulation, with subsequent attempts to psychologically adapt. Out of individual attempts at compensation, arise the signs and symptoms that have been identified with schizophrenia and other psychoses.

While there are a vast number of biological data-banks with long lists of identified genes, neural pathways, intracellular proteins, neuroreceptor variants, and drug target affinities, a master plan relating these components to signs and symptoms of schizophrenia is hard to construct. A

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gene expression/bioinformatics approach in our laboratory yielded many psychosis-related genes [1] but repeat experiments later showed different results. In fact, Ioannidis et al. emphasized that lack of reproducibility is a characteristic of the majority of microarray-based gene expression/bioinformatic profiles [2]. Therefore, a more physiological integrated approach is required.

Brain disturbances & brain supersensitivity to neurotransmitters

Based on the observation that neural abnormalities in the diseased brain often result in behavioral supersensitivity, we focus on the dopamine system and schizophrenia, but our model can apply to any neurochemical transmission system, with the end result being motor symptoms (Parkinson's disease), cognitive symptoms (Alzheimer's disease), or mood symptoms (depression).

The formulation of a supersensitive synapse (where the synaptic response is increased above normal) builds on neurochemical transmission in the nervous system, the existence of which was established by Eccles et al., who studied motor neurons and Renshaw feedback neurons using the Dale principle to prove cholinergic transmission [3]. While neurochemical transmission is the dominant form of interneuron communication, electrical transmission also occurs in some synapses through gap junctions.

There are over 30 animal models of genetic and nongenetic risk factors for psychosis, all showing an elevation in the number of synaptic dopamine D2 receptors that exist in the high-affinity state for dopamine and that influence synapse sensitivity. This set of observations is incorporated into the present model of integrated brain and behavior processes, which is built on the following sequence of events:

- Brain injury
- Synaptic compensation
- Increased neurotransmission
- Subjective awareness of overstimulation
- Psychological adaptation
- Symptom production

This is not a regional or neural circuit model [4-7] but a more general model, because these events can take place anywhere in the brain and can, in the end, produce any number of symptoms and signs, which clinicians subsequently categorize into subsets of neuropsychiatric disorders. The model may be termed the 'supersensitive synapse'.

Outline of the integrated model

The chain of events starts with a nonspecific injury. This can be a gene mutation leading to hypofunction or hyperfunction of a protein. It can be the result of chemicals, toxins, drugs, infectious agents, hypoxia or direct trauma. The original insult to the brain elicits repair mechanisms, which lead to an adaptive change at the level of the synapse. These adaptations are meant to restore equilibrium and, in most instances, they do. However, they can sometimes go too far and lead to supersensitivity (described later). The supersensitive synapse leads to extra neurotransmission and produces a subjective awareness of overstimulation for which the person learns to compensate at a psychological level. It is this secondary compensation that results in signs and symptoms of neuropsychiatric illness. A successful integrative model should provide a direction for treatment, and this, of course, is the hardest part of the task.

Neurotransmission is increased through various neural processes that are called into play to compensate for neuronal injury. These compensatory mechanisms are numerous, graded in effectiveness, and occur in a wide array of synapses. Because our selected example is schizophrenia and because some neuronal loss has been reported in this illness, one could argue that neurotransmission would be diminished rather than increased. But the loss of neurons in schizophrenia is generally minor; in fact, the volume reductions of between 3 and 13% in the schizophrenia cerebral cortex represents a reduction in synapses and neural connections without an actual decrease in total neurons [8]. Even in circumstances where neurons are lost, this does not necessarily mean that neurotransmission is reduced or subsensitive. There is no information on whether abnormalities found in schizophrenia neurons [9,10], increase, decrease, or modify neurotransmission.

Compensation

The principle of neural compensation or adaptation as a root source of the symptoms of psychiatric disease is not new. This principle was proposed by Stevens, based on the histopathology of collateral sprouting of axons and synaptic reorganization following brain lesions.
in epilepsy and Alzheimer’s disease [11]. In response to injury, axons sprout and the synapse is reorganized.

**Axon sprouting**
The compensatory and repair process of axonal sprouting is usually beneficial, but it can also be counterproductive [12]. For example, long-term administration of antipsychotics results in an accumulation of the antipsychotic drug in the substantia nigra with subsequent injury and loss of nigral cells, leading to the clinical signs of tardive dyskinesia [13–15]. However, upon withdrawal of the antipsychotic, the dyskinetic signs usually disappear within a few months in young adults; the symptom alleviation is thought to be based on the sprouting of axon terminals [14]. The initial removal of the antipsychotic, however, makes the dyskinesia temporarily worse, consistent with the idea that partial sprouting results in increased release of neurotransmitter.

**Synaptic changes**
In addition to axon sprouting, there are many changes known to occur postinjury in the affected synapse, some of which reduce neurotransmission, while others lead to supersensitivity and enhanced transmission. The synapse components, listed below, all directly or indirectly modulate neurotransmission. Examples of the components of synaptic transmission are taken from the dopamine system because dopamine synapses have been the most extensively studied in both animals and humans in health and disease [16].

**Neurotransmitter release**
The extent of neurotransmitter release is the most important factor in neurotransmission, and is primarily driven by the frequency of axon firing, which is controlled by neurochemical events occurring upstream of the axon terminals. Naturally, the firing frequencies are driven by multiple feed-forward and feed-backward neural circuits, the combination of which is never constant.

The release of neurotransmitters from nerve axon terminals has a resting component and a nerve impulse-triggered component. The synaptic concentration of the transmitter during rest is of the order of 2 nM in the case of dopamine, transiently going up to 200–400 nM during repetitive axon firing of five pulses per second [17]. Although dopamine is the first transmitter to have its extracellular synaptic concentration precisely examined, the synaptic concentration of serotonin is now also being measured by a similar carbon microelectrode technique [18].

The spontaneous release and the impulse-triggered release of neurotransmitter are not entirely separate events, but are dependent on each other. For example, when methylphenidate is given clinically to reduce symptoms of attention deficit/hyperactivity disorder (ADHD), the drug is thought to act by raising the resting release of the neurotransmitter, which in turn acts on presynaptic receptors to reduce the amount of impulse-triggered transmitter release [19].

**Receptor density**
The number of neurotransmitter receptors per unit volume of a particular brain region has a major influence on transmission. For example, the density of dopamine D2 receptors is elevated by up to 100% in post-mortem human brains from individuals who have died with schizophrenia [20,21]. Such elevations in receptor density have been found in a few studies by PET as well as by single photon tomography in living patients who have never received antipsychotics [22,23] and may explain the clinical dopamine supersensitivity found in most patients with schizophrenia [24].

The density of D2 receptors may influence sensitivity, not only in schizophrenia but may also make Parkinson’s disease patients less sensitive to their daily medication of L-DOPA or other dopamine agonists. For example, Parkinson’s patients who have been taking L-DOPA for years usually require increasing doses of L-DOPA and may also develop dyskinesia. A break in their L-DOPA regimen can re-elevate the D2 density of receptors [25] and re-sensitize the patient to lower doses of L-DOPA [26].

**Transporters for neurotransmitters**
After neurotransmitter molecules are released from nerve terminals, their action is rapidly terminated by rapid diffusion into the extracellular space, by internalization into the postsynaptic neuron, and by rapid re-uptake carriers or transporters located in the presynaptic axon terminals. The density of re-uptake sites or transporters can increase or decrease, with a corresponding alteration in the extent of neurotransmission.

For example, in adults with ADHD, the dopamine transporters are elevated in the right
Receptor-modifying proteins

While each G-linked receptor spans the soap-bubble-thin membrane from the extracellular space to the intracellular cytoplasm, there is a vast number of intracellular proteins that can attach to the receptor and modify its sensitivity to the neurotransmitter.

Such intracellular proteins include the G protein itself, which is composed of α, β and γ subunits. The α subunit binds guanine nucleotides such as the intracellular GDP and GTP. The concentration of GDP in the cytoplasm of many cells is about 10 µM. When GDP attaches to the α subunit, the receptor becomes inactive and exists in a state of low affinity for the transmitter. There are many types of α subunits and γ subunits.

In addition to the variety of G proteins with their different subunits, there is an extensive intracellular network of intracellular proteins that can indirectly influence the sensitivity of the receptors. These proteins include adenylate cyclase, PKA, CREB, DARPP-32 and various ion channels [33]. Ion channels, for example, can electrically influence the resting membrane potential that can alter the sensitivity of membrane-associated receptors to the neurotransmitter.

G-linked receptors can exist in two states

While each of the aforementioned synaptic elements can alter synaptic sensitivity, an important aspect of synaptic sensitivity is dominated by the state of receptor affinity for the transmitter. Each G-linked receptor can exist in a state of low affinity for its neurotransmitter, or in a state of high affinity for the transmitter. For example, in the dopamine D2 receptor, these states are named D2Low and D2High, respectively. The D2High state is very sensitive to the transmitter and responds to nanomolar concentrations of dopamine, while the D2Low state is less sensitive and responds to micromolar concentrations of dopamine. The D2High state is considered to be the physiologically functional state [34]. There is general agreement that D2Low and D2High exist in homogenized tissues in vitro.

There is some controversy about the existence of high affinity states of D2 receptors in vivo. For example, while Skinbjerg et al. [35] did not detect D2High sites in human embryonic kidney cells in culture, Seeman did find D2High sites in rat anterior pituitary adenoma cells in culture [36].

In addition, because low nanomolar concentrations of radioactive dopamine agonists in the bloodstream readily label D2 receptors in human volunteers, these concentrations presumably only label the D2High state of the receptors, thereby supporting the existence of D2High receptors in vivo in humans.
Neuropsychiatric disease & the supersensitive synapse

Suppersensitive synapses are associated with supersensitive behavior and neuropsychiatric disease. (This is a sweeping observation that holds true.) For example, the selective removal or knockout of the metabotropic glutamate-2 or -3 receptor genes leads to animal behavior that is supersensitive to dopamine-like stimulant drugs, accompanied by a marked elevation in the number of D2 receptors in the high-affinity state for dopamine [37]. In addition, other nondopamine genes, when mutated, lead to behavioral dopamine supersensitivity and elevated D2High receptors, including GABA-B1 receptors, trace amine-1 receptors, RGS9 receptor regulator protein, G-protein receptor kinase 6, α1b-adrenoceptors, and postsynaptic density 95 [38,39].

Not surprisingly, dopamine-related genes, when mutated, also lead to behavioral dopamine supersensitivity and elevated D2High receptors, including the dopamine transporter, tyrosine hydroxylase, and catechol-O-methyltransferase. Mutations of genes that do not cause behavioral dopamine supersensitivity do not lead to elevated D2High receptors [38,39].

In addition to gene alterations, long-term exposure of rats to cocaine, amphetamine, methamphetamine, marijuana-like drugs (HU210 and WIN 55,212–2), or quinpirole all induce behavioral dopamine supersensitivity and elevated D2High receptors. While these psychotogenic drugs are known risk factors for inducing psychosis, other risk factors for psychosis also induce dopamine supersensitive behavior in animals and elevate D2High receptors. These factors include hippocampal or entorhinal lesions, social isolation from birth onwards, cholinergic lesions of the cerebral cortex, Cesarean birth with anoxia, and high doses of caffeine. All of the aforementioned risk factors and mutations have been reviewed [40–43], as summarized in Figure 1.

Progressive stages of supersensitivity

There are several stages in the course of development of synapse supersensitivity. For example, in the case of Parkinson’s disease, the loss of nigral cell axon terminals may at first be compensated by an accelerated turnover and release of the transmitter. In later stages, when at least 90% of the nigral terminals are lost, the density of D2 receptors increase, together with an elevation of D2High receptors.

Reversal of supersensitivity

Both the behavioral dopamine supersensitivity and the elevation of D2High receptors were successfully reversed by a D1 agonist [44]. In addition, although antipsychotics such as haloperidol can also induce dopamine supersensitivity and elevated D2High receptors, the administration of haloperidol to animals that already have elevated D2High receptors (induced by amphetamine) reverses and lowers the elevated D2High receptors [41].

The supersensitive synapse template

The palette of components in the supersensitive synapse is composed of all the elements described earlier. The balance of components of this supersensitive synaptic template will vary from synapse to synapse and from brain region to brain region. For example, although D2High receptors are elevated in the striata of dopamine-supersensitive animals, nothing is known about the affinity state of dopamine receptors in the cerebral cortex or the thalamus.

Although the consistent increase in D2High receptors represents a convergence of all risk factors in psychosis, genetic and nongenetic, there is no evidence yet that other types of receptors go into the high-affinity state when synapses become supersensitive. Therefore, the present integrative proposal of a supersensitive synaptic template and its accompanying elevated level of high-affinity receptors is an early attempt at finding a universal explanation for the synaptic pathology that may underlie psychopathology. Such speculation and consistent findings of elevated D2High receptors in dopamine-supersensitive animals need to be tested in schizophrenia volunteers, using PET [42,45].

Behavior & the supersensitive synapse

How does supersensitivity at the level of the synapse lead to clinical symptoms? Exaggerated or inappropriate arm and leg motion, grimacing, tics, repetitive activity and altered reflexes have long been reported to occur in schizophrenia and they are probably direct results of over-transmission at the synapse [46].

Links to cognitive and affective conditions are less direct and require an intermediate step, which, in our model, is again a compensatory one and occurs in each individual at the interpretive and psychological level. Symptoms arise from attempts to deal with stimulus overload.
Withdrawal
The best example of a set of symptoms that are compensatory to overstimulation are the ‘negative’ symptoms of schizophrenia – withdrawal from social roles, relationships and expectations in an attempt ‘to shut out the world.’ Therapists often advise individuals who are suffering from an overwhelming excess of thoughts to take a ‘time out’ of 10 min to do absolutely nothing and to think of nothing. Individuals with schizophrenia often attempt to take such a ‘time out’ in order to reduce their flood of thoughts. The results of that (unconscious) strategy have been labeled anhedonia, avolition, lack of ambition, and isolation by psychiatry, although anthropologists have recognized its adaptive value [47,48].

Auditory hallucinations
The stimulus overload experienced in schizophrenia is often referred to as ‘voices’ in the head. What is specific to schizophrenia is that the voices are seen as coming from the outside. Rather than...
Mood swings

Paranoia

Supersensitive synapses for the chaos and ambiguity that results from the experience of ‘so much going on’ in the head. A paranoid stance shifts the blame from a personal inability to deal with the issue to someone else’s responsibility, an efficient way of preserving self-esteem. Compared with the general population, patients with delusions collect relatively little information about a subject before they ‘jump’ to conclusions [50]. It is a way of substituting certainty (even if objectively wrong) for the chaos and ambiguity that results from supersensitive synapses [51].

Mood swings

The mood of many patients with schizophrenia can oscillate rapidly, with changes from extreme hostility to affability in the course of a brief period. The biochemical basis of mood swings, rapid or slow, is most readily explained by the existence of high- and low-affinity states of the D2 receptor, because D2High and D2Low are quickly interconverted by the metabolism of GDP and GTP within the cell. It should be noted that the two states of D2 are constantly interconverting, and the synaptic and clinical dopamine sensitivity can change in a matter of minutes, depending on factors controlling the metabolism of these two guanine nucleotides. Patients attempt to cope with these oscillations through a variety of means. Routinization, establishing and maintaining routine and structure, is one method. In total, 25% of patients with schizophrenia have been reported to show significant obsessive–compulsive symptoms as a result [52]. Another way of attempting to control mood swings is through the use of mind-altering substances. The supersensitive synapse model enhances the pleasure and reward from nicotine, alcohol and marijuana, reinforcing the use and abuse of these compounds, to which those with schizophrenia are prone. Approximately 50% of patients with schizophrenia develop a co-occurring substance use disorder involving alcohol or illicit substances at some time during their lives [53].

Treatment

In time, we will be able to devise direct methods to deal with the supersensitive synapse [54]. For now, voices and paranoia respond to antipsychotic reversal of the dopamine-supersensitive state and a reduction of D2High receptors [41]. Pharmacological therapies are limited by their many side effects. While behavioral approaches that focus on teaching specific strategies cannot fundamentally change brain function, cognitive rehabilitation (or taking advantage of brain plasticity to train the mind) is a fertile area of therapeutics in schizophrenia and other neuropsychiatric illness [55]. Our model does not yet lead to new treatment strategies but it refocuses our lens on psychiatric symptoms and shows them as serving adaptive ends.

Conclusion

The art of psychiatry is becoming more scientific. For instance, the alleviation of signs and symptoms in schizophrenia generally occurs when 60–70% of brain dopamine D2 receptors are occupied by antipsychotic medications. Future research in schizophrenia, or in the prodrome to schizophrenia, entails an active search for reliable biomarkers. Although considerable data indicate elevations of dopamine D2High receptors in animal models of schizophrenia, the levels of D2High in vivo in animals and in schizophrenia patients are technically difficult to measure. In principle, radioactive dopamine agonists would be expected to prefer attaching to D2High receptors. A biomarker search for elevated D2High receptors in dopamine-supersensitive mice (genetically depleted of dopamine β-hydroxylase) found a rise of 9% in the apparent binding potential for D2High receptors, using only a single dose of intravenous [11C]MNPA [56]. The same study also found an increase of 12% (from 44 to 56%) in the proportion of D2High receptors labeled by [1H] methylspiperone and competed by dopamine [56].
Had the study been done with [3H]domperidone, elevated D2High receptors might more readily have been revealed [38–40].

Although the binding potential of D2High receptors, using the [11C]PHNO agonist, was found to be normal in thirteen untreated schizophrenia individuals [57], a preliminary result for a schizophrenia prodromal subject showed an elevation in D2High receptors, as labeled by [11C]PHNO [58]. Although the cerebellum is often used to define nonspecific binding of the D2 radioligands, it has been reported that approximately a third of [11C]PHNO binding to the cerebellum is to D2 or D3 dopamine receptors [59]. Therefore, in order to see whether D2High receptors are elevated or not, it will be better to use the striatum region as its own control. This can be done by measuring the amount of [11C]PHNO that is displaced by a standard amount of agonist (e.g., N-propynorapomorphine), which should be co-injected at the same time as [11C]PHNO [42]. While one study showed an elevation of [11C]PHNO binding in a prepsychotic subject [58], another study did not find an elevation in 13 schizophrenia patients [57]. It is likely that the latter absence of an elevation in [11C]PHNO binding is because the authors did not measure the displaceable amount of [11C]PHNO, as had been done in a related animal study [42].

Although there are many aspects of mental illness that can be plausibly attributed to alterations in synaptic sensitivity, the leap from test tube to clinic is always hazardous. However, transforming reality, using ‘inner self-talk’, considerably narrowing the scope of one’s life, preferring solitude to the company of others, maintaining control of one’s life by saying “no”, routinizing one’s days, protecting oneself against being duped or humiliated by being constantly on guard can all be readily understood as reactions to the over-stimulation that results from the development of neurotransmitter supersensitivity. Exploring how certain behaviors result from brain alterations in transmitter sensitivity and aid in the task of adaptation can sometimes help to eliminate the problematic behavior. Furthermore, even if it does not, understanding supersensitivity and compensation makes clinicians more empathic and improves therapeutic intervention.

**Future perspective**

Although there will continue to be many more genes found to be associated with schizophrenia, the likelihood of finding a single gene common to the many individuals with schizophrenia is low, primarily because there are so many nongenetic causes of schizophrenia (Figure 1).

The treatment of schizophrenia will be much improved with the development of new ‘fast-off D2’ antipsychotic medications. It was found in 1999 that clozapine dissociated rapidly from brain dopamine D2 receptors in vitro, and it was proposed that a new ‘fast-off-D2’ drug would be clinically like clozapine [60]. Further discussion of this is given elsewhere [61,62]. The first such fast-off-D2 drug has now been tested and found to occupy D2 receptors transiently, with low levels of parkinsonism and prolactin [63,64]. If approved by the various regulatory agencies, the drug is likely to replace clozapine and the associated blood tests, providing much improved treatment of schizophrenia.

While this perspective of dopamine receptors in schizophrenia is naturally incomplete, the present view stems from the fact that the dopamine D2 receptor is the main target for the treatment of schizophrenia, primarily because antipsychotic clinical doses correlate with, and are predicted by, their affinities for the dopamine D2 receptor. In fact, although many non-dopamine-D2 pathways and receptors have been tested as possible antipsychotic drugs, none have succeeded, including antagonists or agonists for:

- Serotonin receptors 2A/2C (MDL100907; SR 46349B)
- D1 receptors (SCH 23390)
- D3 receptors (BP 897)
- D4 receptors (fananserin/sonepiprazole)
- Cannabinoid receptors (rimonabant)
- Neurokinin receptors (SR142801; osanetant)
- Neurotensin receptors (NTS1 antagonist SR48692)
- Ampakine receptors (CX516)
- σ receptors

At present, it appears that, at the least, a D2-blocking component is needed for the treatment of schizophrenia.

The action of an antipsychotic drug has an early onset that often takes effect overnight, as observed by those who first used chlorpromazine clinically. Recent reviews have more rigorously demonstrated that antipsychotic clinical effects have their onset within the first 24 h of
administration, and reach a peak of improvement within the first few days or first week of treatment. While it is true that continued improvement over additional weeks and months occurs, the most rapid rate of improvement occurs within the first week of antipsychotic treatment.

The high rate of improvement within the first few days of antipsychotic treatment strongly suggests that the blockade of receptors is responsible for the improvement of the clinical signs and symptoms of psychosis. The many antipsychotics all have different profiles of receptor blockade, but they all share a common action in blocking D2 receptors at the predicted concentrations in plasma water.

Moreover, antipsychotics such as remoxipride and amisulpiride are highly selective for D2 receptors, largely precluding the contribution of other receptors to clinical effects.

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