



SCHIZOPHRENIA THROUGH THE YEARS

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How historical perceptions and technological innovation have shaped scientists' understanding of schizophrenia.

PSYCHOSIS IN HISTORY

Upon first discovering neurodivergence in people, ancient civilizations turned to spirituality and supernaturalism for answers. Without modern science's understanding of atypical neurological states, Stone Age Egyptians drilled holes in patients' skulls to release 'evil spirits,' a practice that missed the mark for psychiatric treatment, but proves vital millennia later in modern-day neurosurgical practices (Figure 1).¹

As centuries passed, new civilizations popularized the idea that neurochemistry correlated with theistic devotion. Greek mythology and Homeric epics maintained that psychosis was punishment for insufficient worship until Greek physician Hippocrates suggested imbalance of humors as the cause, providing foundational theory for later physicians to build upon.¹

During the Middle Ages, the Christian church adopted Hippocrates' therapeutic techniques of blood-letting, purgatives, and special diets for use alongside prayer and confession. For several centuries, sufferers of psychotic disease were deemed 'heretics' and burned to combat perceived demonic possession until a wave of scientific breakthroughs in the sixteenth century encouraged a shift towards scientific postulation.¹

In 19th century France, physician Philippe Pinel hypothesized a cause for neurodivergence in exposure to psychological and social stressors, advocating for humane treatment and greater respect for patients. In 1910, Swiss psychiatrist Paul Eugen Bleuler coined the term "schizophrenia" to describe the splitting of thoughts from the mind. Decades later, Freud suggested schizophrenia's basis in 'unconscious' conflicts from early childhood, inspiring a new trajectory for schizophrenia research until scientists discovered antipsychotics.¹

DISCOVERING ANTIPSYCHOTICS

Chlorpromazine, the first and most famous anti-psychotic, was first introduced in medicine as an early anesthetic. After its introduction in 1951 by French surgeon Henri Laborit, chlorpromazine effectively stabilized patients without a loss of consciousness, and Laborit sought to repurpose the drug to treat psychosis.²

According to Laborit, chlorpromazine ameliorated patients' otherwise irremediable conditions and prepared patients "to resume



Figure 1: Trepanation. Trepanation is the practice of drilling holes into the skull to relieve ailments. This practice was extremely common in ancient civilizations before technology allowed scientists to attribute symptoms to specific brain regions and surgically intervene with appropriate protocols. A more controlled version of trepanation is used today in neurosurgery when surgeons drill burr holes to relieve pressure or to open the skull to perform surgery. Left, image in public domain; Right, licensed under CC BY-SA 3.0 FR.

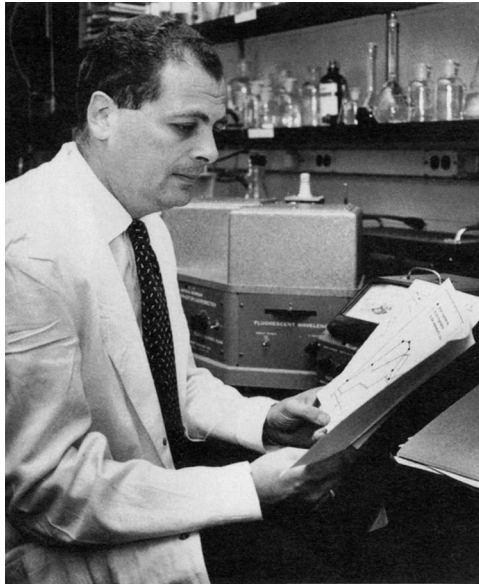


Figure 2: Spectrophotofluorometer. Dr. Sidney Udenfried examining data before the first Aminco-Bowman spectrophotofluorometer by Dr. Robert Bowman. Bowman used the precursor to the bench-top instrument of optical and electrical equipment to assemble the functional spectrophotofluorometer, which allowed scientists to chemically analyze small amounts compounds and has great pharmacological applications to the measurement of neurotransmitters.⁹

normal life,” suggesting it was relatively curative of psychosis. Chlorpromazine’s remarkable stabilizing capabilities, especially when paired with barbiturates and electroshock therapy, were considered a triumph for the burgeoning field of psychopharmacology.^{2,3}

Although chlorpromazine’s mechanisms of action remained unknown to Laborit, further research led to an explosion of scientific discovery in psychopharmacology and neuroscience. By the end of the decade, scientists had identified many neurotransmitters, including serotonin and dopamine. Electron microscopy clarified the nature of synaptic transmission between neurons as chemically-mediated and the spectrophotofluorometer enabled precise chemical analysis of neurotransmitters in the brain (Figure 2).^{2,4,5} Together, these new developments led to clinical research that attributed chlorpromazine’s antipsychotic abilities directly to its anti-serotonin and

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anti-dopamine effects.²

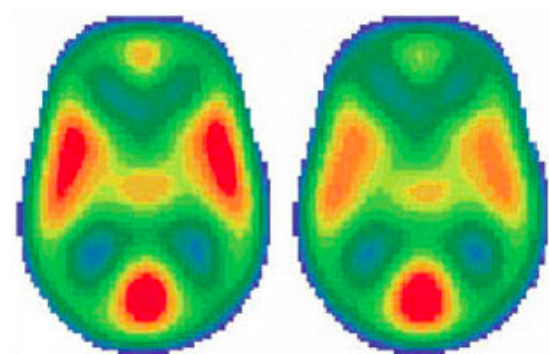
Antipsychotics research centered on serotonin until Arvid Carlsson demonstrated that blocking dopamine receptors causes antipsychotic effects, shifting the focus to dopamine in 1963.² Following this shift, schizophrenia research aimed to elucidate the mechanisms by which dopamine causes psychosis, eventually progressing through three distinct versions of the Dopamine Hypothesis.

THE DOPAMINE HYPOTHESIS

VERSION I: TARGETING THE DOPAMINE RECEPTOR

After Carlsson’s 1963 discovery, dopamine receptors were the targets of schizophrenia research. Dopamine’s involvement was further underscored when Carlsson found that reserpine, a chemical derivative of an Indian treatment for insanity, reduced dopamine stores in synaptic vesicles

Figure 3: PET scans of schizophrenic and healthy patients. Positron Emission Tomography (PET) is a neuroimaging technique is used to compare and visualize activity in different regions of the brain. Blood flow brings oxygen and nutrients necessary for ATP synthase to brain tissue, and can thus be used as a measure of brain activity. PET scan of schizophrenia patient (left) shows more brain activity in the temporal lobes of the brain, another site of D2 dopamine receptors, when compared to that of a healthy patient (right).¹⁰



“Emphasizing dopamine dysregulation’s involvement in psychosis, the team drew an important distinction between schizophrenia, the broader neurodevelopmental disorder, and psychosis, one of its symptoms.”

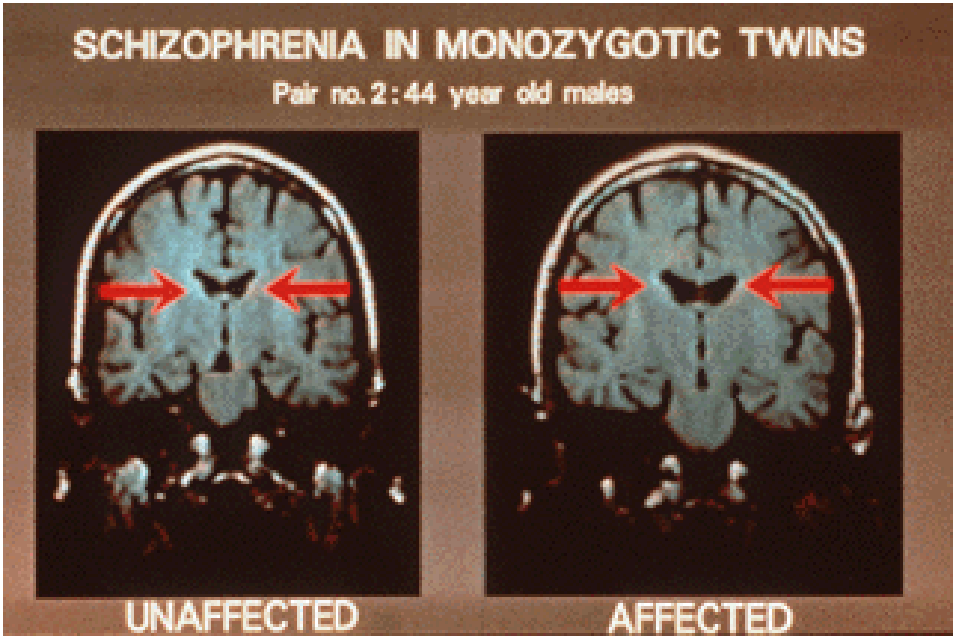


Figure 4: MRI scans of healthy and schizophrenic patients. Neuroimaging techniques such as Magnetic Resonance Imaging (MRI) enable scientists and clinicians to quickly and efficiently recognize abnormalities in brain structure and, at times, attribute them to neurological disorders. MRI aligns protons in brain tissue with a magnetic field to visualize brain anatomy. The MRI of the affected twin shows enlarged ventricles, which is associated with schizophrenia for unknown reasons, signifying how much else remains to be explored.

of neurons. Later, Carlsson discovered that chlorpromazine did not affect these dopamine stores, instead blocking serotonin, noradrenaline, and primarily dopamine receptors.⁶

In 1977, Carlsson established that dopaminergic hyperfunction produced symptoms of paranoid schizophrenia.⁷ Afterwards, scientists blocked dopamine receptors to fight schizophrenia, but had yet to attribute mechanisms to positive, negative, and cognitive symptoms or localize the abnormality to a specific region of the brain.

VERSION II: LOCALIZING THE ABNORMALITY

In version II, however, scientists localized dopaminergic hyperactivity to D2 dopamine receptors in the striatum and connected an additional facet, D1 dopamine hypoactivity, to the frontal cortex.

Following the 1977 invention of Positron Emission Tomography (PET), PET studies revealed hypoactivity and low dopamine metabolites in the frontal cortex of schizophrenia patients (Figure 3). In 1980, scientists connected the aforementioned cortical hypoactivity to

subcortical hyperactivity at D2 receptors in the striatum.⁸

Together, this D1 hypodopaminergia and D2 hyperdopaminergia likely resulted in negative and positive symptoms of schizophrenia, respectively. However, there was still no framework to explain how subcortical hyperdopaminergia led to delusions or how cortical hypodopaminergia resulted in a depressive affect.

VERSION III: THE FINAL COMMON PATHWAY

In the following decades, scientific innovation revolutionized scientists’ means of studying psychiatric disease. Recent findings involve synaptic plasticity, the malleable nature of the synapse.⁹ To enable this malleability, extrasynaptic receptors located further from the synapse regulate neurotransmitter release in a feedback-mediated system.¹⁰ Accordingly, extrasynaptic D2 receptors modulate dopamine release based on nearby dopamine levels.⁶

In 2006, Carlsson attributed schizophrenic dopamine dysfunction to malfunction in dopaminergic synapses and a poorly compensating feedback-mediated

system, suggesting that defective synapses “[lead] to feedback activation and the resulting observed increase in dopaminergic tone.”⁶

Initially, defective dopaminergic synapses cause low dopamine concentrations. To compensate, extrasynaptic transmission increases, causing psychosis. Failing to reach the synapse in a controlled fashion, extrasynaptic transmission compensates poorly for the defect, and original low dopamine levels cause negative symptoms.⁶

In 2009, scientists Oliver Howes and Shitij Kapur proposed that several different stimuli—including genetics, stress, drugs, and the dopamine dysfunction detailed in version II—lead to D2 dopamine dysregulation. Emphasizing dopamine dysregulation’s involvement in psychosis, the team drew an important distinction between schizophrenia, the broader neurodevelopmental disorder, and psychosis, one of its symptoms.⁸

CONCLUSION

Throughout history, physicians failed to rationalize psychosis without demonizing patients, and could not attribute its basis to neurochemistry. As innovation fueled scientific discovery, scientists' means to explore the once-concealed secrets of the mind broadened dramatically. Technological innovations such as electron microscopy, spectrofluorimetry, and neuroimaging have revolutionized modern science's ability to understand psychiatric diseases (Figure 4).

With modern science's understanding of psychosis, schizophrenia is now considered a biological brain disorder. Medications that are the product of decades of cutting-edge clinical research allow most patients to lead normal lives.⁶ While early scientists had no choice but to blindly try and err, present-day scientists have access to cellular minutia and effective medications to treat schizophrenia better than ever before.

After understanding dopamine's role in schizophrenia, pharmacologists synthesized several medications to categorically account for hallucinations and delusions.⁶ Yet, some facets of the complex brain disorder remain unknown. Future directions for schizophrenia research include reducing side-effects of medications, such as tardive dyskinesia and cardiac arrhythmia; and targeting cognitive and negative symptoms, namely working memory deficits, depressive affect, and social withdrawal.¹¹

Despite science's deepened understanding, schizophrenia remains highly stigmatized. On average, desire for distance from individuals with schizophrenia increased from 1996 to 2006, largely due to perceived dangerousness.¹² Society's time-honored tradition of demonizing neurodivergent people appears to have persisted into the 21st century. As science resolves the remaining limitations of schizophrenia treatment, one can only hope that society will resolve its remaining stigma to allow neurodivergence to be appreciated, not feared.

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