HX	Historical and Foundational Knowledge of Mental Illness
THEO	Pathologic Theories of Schizophrenia
SET	Treatment Settings
EPI	Epidemiology
ANA	Anatomy & Pathology
DX	Diagnosis
NAT	Natural History/Course
PHE	Phenomenology
TX	Treatment
IMA	Brain Imaging
PHYS	Neurophysiological Measures
GEN	Genetics

ANCIENT WORLD – MIDDLE AGES			
HX	**PreHX**	**Mental Illness Caused by Supernatural or Spiritual Entities**[1]	Samuel 16:14, 23 (KJV)
HX	**400BC**	**Early Scientific Theories of Mental Illness**	
HX	*400BC*	Humoral theory of mental illness: Result of an imbalance in the body's four fluids, or humors[2]	Hippocrates (c.460-357 BC)
HX	*100-200AD*	Brain-based theory of mental disturbances: Association of brain with mental functions and behavior[3]	Galen (129 AD-210AD)
HX	**1563**	**Mental Illness Caused by Spirits, Moral Deviance, Religious Heresy** Moral, social, and religious causes of mental illness[4]	Johann Weyer
HX	**1628**	**Foundation of Medical Biology** First detailed description of the circulatory system: heart, blood vessels, and blood being pumped to organs including the brain[5]	William Harvey 1578-1657
18th CENTURY			
HX	**1778**	**Prescientific Theories of Mental Illness**	-----
HX	*1778*	Animal magnetism theory of mental illness[6]	Franz Mesmer (1734-1815)
HX	*1789*	Phrenology theory of brain anatomy & function[7]	Franz Joseph Gall (1786-1828)
THEO	**1778**	**Conceptualized Mental Illness as Naturally Occurring Condition**[8]	Philippe Pinel (1745-1826); 1798, *Nosographie psilosophique*
SET	**1792**	**Asylum Movement & Moral Treatment**	
SET	*1792*	Removal of iron chains & moral therapy: Removed the iron chains from asylum patients and established a therapeutic environment[9]	Philippe Pinel (1745-1826) - *Nosographie philosophique (1807)*, *A treatise on insanity (1806)*,
SET	*1796*	Establishment of York Retreat: Pioneered moral treatment[10]	William and Samuel Tuke (1784-1857)
SET	*1841*	Asylum reform movement led by Dorothea Dix begins[11]	Dorothea Dix (1802-1887)
19TH CENTURY			
EPI	**1840**	**1840 U.S. Census: First Assessment of Frequency of Mental Illness** Rates of mental illness and developmental disabilities[12]	Deutsch, 1944
ANA	**1861**	**Postmortem Studies of Brain Anatomy & Neuropathology**	-----
ANA	*1861*	Mapped the brain's anatomy, defining the regions responsible for different forms of aphasia: Expressive aphasia described by Paul Broca (Broca's aphasia). Described first model of the neuropsychology of language[13]	Paul Broca (1824-1880)
ANA	*1868*	Constructed histologic atlas of the brain, defined sensory cortex rostral to central fissure[14]	Theodor Meynert (1833-1892)
ANA	*1874*	Mapped the brain's anatomy, defining the regions responsible for different forms of aphasia: Fluent aphasia and receptive aphasia described by Carl Wernicke (Wernicke's aphasia)[15]	Carl Wernicke (1848-1905)
ANA	*1892*	Described fronto-temporal dementia (Pick's disease)[16]	Arnold Pick (1851-1924)
ANA	*1906*	Identified the senile plaques and neurofibrillary tangles, now known as the hallmarks of Alzheimer's disease[17]	Alois Alzheimer (1864-1915)
ANA	*1909*	Established a cartography of the brain into functional anatomical regions[18]	Korbinian Brodmann (1868-1918)
ANA	*1915*	Described pathomorphology in postmortem brains of schizophrenia: Found structural pathology in 90% of schizophrenia cases; e.g., moderate general or focal atrophy, and internal hydrocephalus[19]	Southard, 1915, 1919

HX	**1873**	**Foundation of Modern Neuroscience**	-----
HX	*1873*	Development of Golgi Stains that enabled cells embedded in the brain's matrix to be clearly visualized[20]	Golgi 1873 & 1874
HX	*1888*	Development of the Neuron Doctrine: the brain was composed of anatomically distinct processing units, or neurons; described and illustrated brain cell types[21]	Ramon y Cajal 1888, 1889, & 1894
DX	**1891**	**Definition of Dementia Praecox[22]** Identified illness now called schizophrenia. Creation of a nosology of mental illness	Pick 1891, Kraepelin 1896
NAT	**1896**	**Catamnestic Studies of Schizophrenia** Described the different trajectories of the natural history of schizophrenia	-----
NAT	*1896*	Described clinical progression of illness[23]	Kraepelin 1896
NAT	*1973*	Gender differences in course of schizophrenia[24]	Angst et al., 1973 (book)
NAT	*1976*	Described different courses of illness[25]	Ciompi & Muller, 1976 (book); Bleuler, 1978 (book)
		20TH CENTURY	
DX	**1908**	**Dementia Praecox Redefined as Schizophrenia[26]** Changed name and definition of schizophrenia	Bleuler 1908, 1911
PHE	**1911**	**Symptoms**	-----
PHE	*1911*	Primary and accessory symptoms[27]	Bleuler, 1911 (book)
PHE	*1966*	First rank symptoms[28]	Schneider, 1966 (book)
PHE	*1974*	WHO international pilot studies described schizophrenia orthogonal symptom dimensions: Distinguished independent dimensions of pathology in schizophrenia, demonstrated that psychotic symptoms were not pathognomonic to schizophrenia[29]	Strauss and Carpenter
PHE	*1974*	Recognition of nonpsychotic symptom dimensions of schizophrenia: Concept of primary and secondary negative symptoms[30]	Carpenter, Straus, & Bartko (1974)
PHE	*1982*	Integrated clinical phenomenology and pathophysiology: Concept of positive and negative symptoms, associated with excess and diminished dopamine activity[31]	Crow et al.
PHE	*1982*	Defined negative symptom items & developed rating instrument: Increased emphasis on negative symptoms in clinical profile of schizophrenia and provided a method to assess them[32]	Andreasen
DX	**1913**	**Discovered Cause of General Paresis of the Insane[33]** Isolated the spirochete that caused neurosyphilis in postmortem brain tissue	Noguchi & Moore
THEO	**1916**	**Early Heuristic Theories of Schizophrenia**	-----
THEO	*1916*	Genetic theory of schizophrenia: Based on theory of degeneration and family studies[34]	Ernst Rüdin (link)
THEO	*1962*	High emotional expression in the family triggers psychotic symptoms of schizophrenia[35]	Brown et al.
THEO	*1962*	Stress-Diathesis Model: Stress triggers the onset of schizophrenia in vulnerable individuals[36]	Meehl Zubin & Spring
TX	**1918**	**Somatic Treatments of Schizophrenia**	-----
TX	*1918*	Malaria therapy: Hyperthermia treatment for general paresis of the insane[37]	Wagner-Jauregg 1918
TX	*1936*	Psychosurgery[38]	Moniz 1936 & 1937
TX	*1939*	Development of electroconvulsive therapy: Effective in treating schizophrenia but considered invasive, expensive, and complicated[39]	Cerletti and Bini, 1938
IMA	**1927**	**In-Vivo Structural Brain Abnormalities**	-----
IMA	*1927*	Pneumoencephalography/In-Vivo Imaging Studies of Brain Morphology: First identifiable physical abnormality in the brain associated with mental illness[40]	Jacobi & Winkler, 1927;

IMA	*1976*	First CT study of schizophrenia in U.K., showing ventricular enlargement[41]	Johnstone et al., 1976,
IMA	*1979*	First CT study of schizophrenia in U.S., showing ventricular enlargement[42]	Weinberger et al., 1979
IMA	*1989*	First MRI study of temporal lobe volume abnormalities in schizophrenia[43]	Johnstone et al., 1989; Rossi et al., 1989, Suddath et al., 1989
IMA	*1990*	MRI studies demonstrating gray matter volume abnormalities in schizophrenia[44]	Andreasen et al., 1990
IMA	*1990*	First twin study with MRI: Demonstrated genetic and environmental contributions to schizophrenia susceptibility[45]	Suddath et al., 1990
IMA	*1990*	In-vivo imaging demonstration of reduced size of the hippocampus: First report with structural MRI abnormal medial temporal lobe morphology in patients at the onset of their illness[46]	Bogerts et al., 1990;
IMA	*1993*	In-vivo imaging demonstration of reduced size of the hippocampus: Reduced volume of the hippocampal formation in chronic schizophrenia patients[47]	Bogerts B, et al 1993
IMA	*1994*	MRI study demonstrates enlargement of caudate nuclei in schizophrenia was due to first generation APD treatment[48]	Chakos et al., 1994
IMA	*1998*	MRI study demonstrates reduced volume of caudate nuclei in treatment-naive patients with schizophrenia[49]	Keshavan et al 1998
EPI	**1934**	**Environmental Effects on Risk of Schizophrenia**	
EPI	*1934*	Obstetrical complications[50]	Rosanoff et al., 1934; Verdoux et al., 1997; Cannon et al., 2000
EPI	*1965*	Social environment/ethnicity/migration[51]	Kiev, 1965; Mirsky et al., 1985; Mallet et al., 2002; Cannon et al., 2003 (book chapter); Sharpley et al., 2001
EPI	*1983*	Paternal age[52]	Kinnell, 1983; Malaspina et al., 2001
EPI	*1987*	Drug abuse[53]	Andréasson et al., 1987; Murray et al., 2003 (book chapter)
EPI	*1988*	Infections/pathogens[54]	Mednick et al., 1988; Suvisaaari et al., 1999; Brown et al., 2001; Bagalkote et al., 2001; Buka et al., 2001; Koponen et al., 2004; Arias et al., 2012
EPI	*1998*	Maternal stress[55]	Susser et al., 1998; van Os & Selten, 1998; McGrath, 1999; Kinney, 2001
EPI	*2011*	Nutritional effects[56]	McGrath et al., 2011
PHYS	**1938**	**Neurophysiologic Manifestations of Schizophrenia**	-----
PHYS	*1938*	EEG Studies: Demonstrated sensory processing deficits in schizophrenia[57]	MacMahon & Walter, 1938; Blum, 1957; Salamon & Post, 1965; Umbricht et al., 2006; Thomas et al., 2016
PHYS	*1973*	ERP Studies: Demonstrated biologic features of schizophrenia[58]	Levit et al., 1973; Pfefferbaum et al., 1989; McCarley et al, 1993
PHYS	*1973*	Eye-tracking studies: Demonstrated (epiphenomenal) biologic features of schizophrenia; eye-tracking dysfunction widely replicated in schizophrenia and is overrepresented in clinically unaffected first-degree relatives[59]	Holzman, 1973, 1974, 1977; Levy et al., 2010
PHYS	*1991*	Mismatch negativity: Demonstrated biologic features in high-risk individuals[60]	Shelley et al, 1991; Javitt et al, 1993
PHYS	*2000*	Decreased neuronal synchrony and gamma-band activity in schizophrenia[61]	Haig et al 2000 Spencer et al 2003
GEN	**1938**	**Epidemiologic Genetic Studies**	-----
GEN	*1938*	Schizophrenia more frequent in family members of patients[62]	Kallmann, 1938 (book)
GEN	*1946*	Twin studies show increased concordance for schizophrenia among monozygotic compared with dizygotic twins[63]	Kallmann, 1946
GEN	*1958*	The Monogenic Theory of Schizophrenia[64]	Slater, 1958

GEN	*1966*	Adoption studies of offspring of people with schizophrenia found genes had greater effect than environment [65]	Karlsson, 1966; Heston, 1966
GEN	*1967*	A Polygenic Theory of Gottesman and Shields[66]	Gottesman & Shields, 1967
GEN	*1987*	Sporadic vs. familial schizophrenia[67]	Lewis et al., 1987; Kendler, 1987
GEN	*1998*	22q11 Deletion Syndrome identified as a genocopy of schizophrenia[68]	Bassett & Chow, 1999, Basset et al., 1998
TX SET	**1943**	**Clubhouse Movement Established in the U.S.[69]** Clubhouse care model began when discharged patients from Rockland Psychiatric Center formed the "We Are Not Alone" group to support each other and met on the steps of the New York Public Library	Fountain House, 1999; McKay et al., 2016
TX SET	*1948*	Fountain House established with philanthropic support on West 47th Street, New York City	Fountain House, 1999
20TH CENTURY (continued)			
TX	**1949**	**Pharmacologic Treatments of Schizophrenia**	-----
TX	*1949*	Discovery of chlorpromazine (CPZ): Development of antipsychotic drugs (APDs)[70]	Charpentier 1947; Laborit 1949
TX	*1952*	First demonstrations of efficacy of CPZ: Proof of efficacy and safety in Europe and U.S.[71]	Delay, Denniker, & Harl, 1952a & 1952b; Lehmann & Hanrahan, 1954
TX	*1957*	Neurological adverse effects of CPZ: Description of side effects of antipsychotics (extrapyramidal symptoms, tardive dyskinesia, tardive dystonia)[72]	Lambert et al, 1959; Schoenecker, 1957; Simpson et al., 1964
TX	*1971*	First use of long-acting injectable (LAI) medicine: LAI APDs reduce nonadherence and relapse[73]	Denham & Adamson, 1971; Hogarty et al., 1974; Davis, 1975
TX	*1974*	Clozapine, first atypical APD: Studies of efficacy and safety in schizophrenia patients[74]	Gerlach et al., 1974; Shopsin et al., 1979; Kane et al., 1988;
TX	*1975*	Discovery of clozapine's serious adverse effects (agranulocytosis, myocarditis)[75]	Idänpään-Heikkilä et al., 1975; Anderman et al., 1977; Alvir et al., 1993
TX	*1988*	Study shows clozapine's superior efficacy in treatment-refractory patients[76]	Kane et al., 1988
TX	*1991*	Introduction of second-generation (atypical) APDs[77]	Moller et al., 1991; Marder & Meibach, 1994; Beasley Jr et al., 1996
TX	*1992*	Metabolic syndrome (weight gain, high blood pressure/cholesterol/triglycerides/glucose)[78]	Allison et al., 1999; Newcomer, 2005 McEvoy et al., 2007; Fleischhacker et al, 2008
TX	*2003*	Studies demonstrated clozapine's efficacy in preventing suicide[79]	Meltzer et al., 2003
TX	*2020*	First non-D-2 receptor targeted drug treatments for schizophrenia: SEP363856 (TAAR-1 agonist) and xanomeline/trospium (M1M4 agonist)[80]	Koblan et al., 2020 & Brannan et al., 2020
TX	**1952**	**Psychosocial Treatments for Schizophrenia**	-----
TX	*1952*	Cognitive behavioral therapy[81]	Beck, 1952; Bentall, Haddock, & Slade, 1994; Kupiers et al., 1997; Tarrier & Wykes, 2004; Wykes et al., 2008
TX	*1976*	Social skills training[82]	Bellack et al 1976; Kurts & Mueser, 2008
TX	*1978*	Case management[83]	Altshuler & Forward, 1978
TX	*1980*	Psychoeducation[84]	Anderson et al., 1980
TX	*1993*	Cognitive remediation[85]	Green, 1993; Medalia et al., 1998; Medalia & Choi, 2009; Medalia & Saperstein, 2013
TX	*1994*	Supportive employment[86]	Drake et al., 1994; Chandler et al., 1996
DX	**1958**	**Drug-Induced Schizophrenia**	-----
DX	*1958*	Chronic psychostimulant use induces sustained schizophrenia[87]	Sato et al., 1982; Sato, 1986

DX	*1992*	Chronic PCP use induces sustained schizophrenia[88]	Rainey & Crowde, 1975; Allen & Young, 1978
TX SET	**1963**	**Community Mental Health Act Passed[89]** Legislation that stimulated deinstitutionalization	President John F. Kennedy
EPI	**1969**	**Comparison of Diagnostic Practices in U.S. & U.K. Demonstrates Unreliability of Diagnoses[90]** Demonstrated unreliability and questioned the validity of schizophrenia diagnosis	Cooper et al., 1969
DX	**1972**	**Formulation of Operational Criteria for Diagnosis of Mental & Substance Use Disorders**	-----
DX	*1972*	Feigner Criteria (Washington University Academic Psychiatry Department)[91]	Feighner et al., 1972
DX	*1974*	Present State Exam; CATEGO Algorithm (U.K. Academic Group)[92]	Wing et al., 1974
DX	*1978*	Research Diagnostic Criteria (Columbia University Academic Psychiatry Department)[93]	Spitzer et al., 1978
DX	*1980*	DSM-III: Formal codification by APA for clinical use and alignment with ICD system[94]	DSM-III
IMA	**1974**	**Functional Brain Abnormalities**	-----
IMA	*1974*	Hypofrontality: Reduced cerebral blood flow in frontal cortex resting state[95]	Ingvar & Franzen, 1974
IMA	*1984*	Hypoactivation of frontal cortex on Wisconsin Card Sort activation[96]	Weinberger, Berman, 1986
IMA	*1986*	PET studies determined D-2 occupancy levels of antipsychotics at therapeutic dosing[97]	Farde et al., 1989; Farde L, et al. 1990; Wong et al., 1986
IMA	*1996*	SPECT & PET demonstrate dopamine dysregulation: First direct in vivo confirmation of the dopamine hypothesis (found excess striatal dopamine release)[98]	Laurelle et al., 1996; Brier et al., 1997; Laurelle et al., 1999, Abi-Dargham et al., 2000
IMA	*1996*	Functional imaging studies demonstrated increased neural activity in CA1 region of the hippocampal formation in schizophrenia subjects[99]	Heckers et al., 1998 Medoff et al., 2001 Schobel et al. 2009, 2013
IMA	*2001*	fMRI studies demonstrated working memory/executive function deficits in schizophrenia[100]	Perlstein et al., 2001
IMA	*2010*	PET studies found dopamine dysregulation in associative striatum (rather than mesolimbic dopamine excess)[101]	Kegeles et al., 2010
IMA	*2014*	fMRI/resting state & connectivity: Identified network abnormalities in schizophrenia within the frontoparietal control network[102]	Baker et al., 2014
IMA	*2014*	fMRI/resting state & connectivity: Identified cortical microcircuit dysfunction (disruption of E/I balance in prefrontal cortex) underlies working memory impairment in schizophrenia[103]	Murray et al., 2014
IMA	*2017*	fMRI/resting state & connectivity: Identified brain circuit that mediates hallucinations, using functional neuroimaging and computational modeling of perception[104]	Powers, Mathys, & Corlett, 2017
THEO	**1974**	**Dopamine Hypothesis**	-----
THEO	*1974*	First scientifically credible pathophysiological theory of schizophrenia, based on the actions of APDs and stimulants. Dopamine hyperactivity in the mesolimbic pathway[105]	Snyder et al. 1974; Seeman & Lee, 1975; Burki et al 1975; Meltzer & Stahl, 1976; Carlsson, 1978
THEO	*1980*	Biphasic (mesolimbic & mesocortical) model of dopamine[106]	Pycock et al., 1980; Carlsson, 1988; Weinberger et al 1987; Davis et al., 1991
THEO	*1997*	Neurochemical sensitization of dopamine systems[107]	Lieberman et al., 1997; Laruelle & Abi-Dargham, 1999
THEO	*2003*	Salience model of dopamine pathophysiology[108]	Kapur, 2003; Howes & Kapur 2009
PHE	**1977**	**Cognitive Impairments**	-----
PHE	*1977*	Identified attentional disturbances in schizophrenia as symptom of the illness[109]	Nuechterlein, 1977

PHE	*1978*	Impairment of cognitive functions as a core pathologic dimension of schizophrenia: Used neuropsychological test battery to demonstrate range of cognitive deficits[110]	Heaton et al., 1978
PHE	*1987*	Wisconsin Card Sort Test demonstrates executive function deficit[111]	Goldberg et al.
PHE	*1990*	Discordant monozygotic twin study shows greater cognitive deficits in affected twins: Demonstrates genetic and environmental contributions to schizophrenia[112]	Goldberg et al., 1990
PHE	*1994*	Demonstrated cognitive impairment in first-episode patients: First-episode patients already have cognitive impairments[113]	Saykin et al., 1994; Bilder et al., 2000
PHE	*1996*	Demonstrated relationship between cognitive impairment and functional capacity: Functional significance of cognitive deficits[114]	Green, 1996
PHE	*1999*	Demonstrated severe dementia in elderly chronically ill schizophrenia patients: Dementia of dementia praecox[115]	Harvey et al., 1999
PHE	*2014*	Demonstrated working memory & reinforcement learning deficits: Integration of working memory and reward sensitivity[116]	Collins et al., 2014
20TH - 21ST CENTURIES			
IMA	**1980**	**Longitudinal Brain Abnormalities**	-----
IMA	*1980*	Longitudinal study of schizophrenia patients with pneumoencephalography showed progression in ventricular size[117]	Huber et al., 1980
IMA	*1991*	MRI studies showed progressive brain morphologic changes over the course of schizophrenia[118]	Degreef, et al., 1991; Lieberman et al. 1992, 2001, 2005a & 2005b; DeLisi et al. 1997; Gur et al. 1998; Lawrie et al., 1999; Pantelis et al., 2003; Andreasen et al. 2011; Cahn et al. 2002, 2006, 2009; Bartzokis et al., 2012
IMA	*2009*	Hippocampal CA1 cerebral blood flow and volume: Elevated left CA1 cerebral blood volume at baseline predicts transition to syndromal psychosis and hippocampal atrophy[119]	Schobel et al. 2009, 2013
TX	**1980**	**Models of Care**	-----
TX	*1980*	Assertive community treatment[120]	Stein & Test, 1980
TX	*1992*	Early intervention[121]	Falloon, 1992
TX	*2000*	Assisted outpatient treatment[122]	Swanson et al., 2000
TX	*2015*	RAISE Studies: Coordinated specialty care of first-episode psychosis shown to improve outcome[123]	Dixon et al., 2015; Kane et al., 2016
NAT	**1981**	**Treatment Outcomes of First-Episode** Prospective studies of early stages of schizophrenia demonstrated good treatment response, reduction of duration of untreated psychosis, feasibility, and efficacy of specialized treatment programs	-----
NAT	*1981*	High rates of treatment response in first-episode patients at lower doses of APD medications[124]	May et al., 1981; Lieberman et al., 1992; McEvoy et al., 1991
NAT	*1991*	Duration of untreated illness correlates with treatment outcome[125]	Wyatt 1991, Loebel et al 1992
NAT	*2004*	TIPS study demonstrates feasibility of reducing the duration of untreated 2004 illness to improve outcome[126]	Melle et al., 2004
NAT	*2015*	LAI treatment in recent-onset schizophrenia patients prevents relapse compared with oral medication and possible evidence of neuroprotection[127]	Subotnik et al., 2015; Stevens et al., 2016
PHE	**1982**	**Schizophrenia Subtypes**	
PHE	*1982*	Two syndrome topology of schizophrenia[128]	Crow et al.
PHE	*1987*	Kraepelinian schizophrenia subtype: Defined based on symptoms, course, and biologic features (e.g., brain morphology, frontal blood flow)[129]	Keefe et al; Buchsbaum et al., 2002
PHE	*1988*	Deficit state subtype, defined based on negative symptoms[130]	Carpenter et al., 1988
THEO	**1983**	**Neurodevelopmental Hypotheses of Schizophrenia**	-----

THEO	*1983*	Synaptic Pruning Hypothesis[131]	Feinberg, 1982;
THEO	*1987*	Neurodevelopmental Hypothesis[132]	Weinberger, 1987; Murray & Lewis, 1987; Bloom 1993, Keshavan et al., 1994
EPI	**1984**	**Epidemiologic Studies of Schizophrenia**	-----
EPI	*1984*	WHO Study of Population Frequencies of Schizophrenia: Epidemiologic studies in 10 countries utilizing objective diagnostic criteria[133]	Jablensky et al., 1992
EPI	*1994*	Epidemiologic Catchment Area Study: Epidemiologic study of U.S. rates of mental illness[134]	US Dept of Health & Human Services, 1994
ANA	**1984**	**Neuropathology of Schizophrenia**	-----
ANA	*1984*	Abnormalities in hippocampus cytoarchitecture in CA1, CA2, subiculum subfields in schizophrenia patients: Postmortem studies showed neuronal disarray[135]	Kovelman & Scheibel, 1984;
ANA	*1985*	Reduced volume of the hippocampus[136]	Bogerts, Meerts, & Schonfeldt-Bausch, 1985
ANA	*1998*	Absence of neurodegeneration and neural injury in postmortem brains in schizophrenia: Militates for neurodevelopmental and against neurodegenerative theory[137]	Arnold et al., 1998
ANA	*1998*	Pathology in cell processes & neuropil: Reduced cortical dendritic length and spine density[138]	Garey et al., 1998; Glantz & Lewis, 2000; Rosoklija et al., 2000;
ANA	*1999*	Pathology in neuronal subtypes: GABA dysfunction of interneurons in hippocampus and frontal cortex[139]	Benes, 1999; Lewis et al., 1999; Benes & Berretta, 2000; Lewis, 2000; Benes & Berretta, 2001
ANA	*1999*	Neuropil hypothesis of schizophrenia: Reduction in focal cortical volume due to neuropil not cell bodies[140]	Goldman-Rakic & Selemon, 1999
THEO	**1987**	**Glutamate Hypothesis**	-----
THEO	*1987*	Glutamate Hypothesis: Heuristic pathophysiological theory of schizophrenia[141]	Robinson, M. B., & Coyle, J. T. (1987). Javitt & Zukin, 1991; Krystal et al., 1994; Olney & Farber 1995; Javitt et al., 1996; Umbricht et al., 2000; Goff & Coyle, 2001; Krystal et al., 2005; Moghaddam & Javitt, 2012; Schobel et al. 2013
THEO	*1990*	Integration of Dopamine and Glutamate Theories: Formulation of a pathophysiological theory that merges the dopamine and glutamate theories[142]	Carlsson & Carlsson, 1990; Kegeles et al., 2000; Balla et al., 2001; Laurelle, Kegeles, & Abi-Dargham, 2003; Javitt, 2007; Kantrowitz & Javitt, 2010;
THEO	*1991*	PCP Model of Schizophrenia implicates NMDA receptor hypofunction correction[143]	Javitt, D. C., & Zukin, S. R. (1991)
THEO	*1998*	NMDA antagonism increases synaptic glutamate[144]	Bergeron et al., 1998; Abi-Saab et al., 1998; Moghaddam & Adams, 1998; Lahti et al., 1999; Krystal et al., 1999
THEO	**1991**	**Neurodegenerative Hypothesis of Schizophrenia** Heuristic pathophysiological theory of schizophrenia based on clinical neuroimaging studies of the progressive course of the illness, inspiring early detection and intervention research[145]	DeLisi et al., 1997; Lieberman, 1999, 2001, 2017
TX	**1997**	**Reduced Life Expectancy of Schizophrenia Patients**	-----
TX	*1997*	Due to medical comorbidities and suicide[146]	Brown, 1997; Saha et al., 2007
TX	*2007*	Associated with lack of APD treatment[147]	Tiihonen et al., 2007
DX	**2001**	**Autoimmune Encephalitis[148]** Autoimmune disorders affecting brain function can mimic schizophrenia	Buckey et al., 2001; Dalmau et al., 2008
GEN	**2008**	**Molecular Genetics**	
GEN	*2008*	Rare chromosomal deletions and duplications increase risk of schizophrenia[149]	International Schizophrenia Consortium, 2008
GEN	*2009*	The first positive evidence of schizophrenia polygenes[150]	International Schizophrenia Consortium, 2009; Ripke et al., 2014
GEN	*2012*	Genomewide Association Study (GWAS) on schizophrenia uses Genomewide Complex Trait Analysis to infer presence of polygenes[151]	Richards et al., 2012; Lee et al., 2012

GEN	*2012*	Copy number variation (CNV) in psychiatric genetics[152]	Lee et al., 2012
GEN	*2014*	Polygenic burden of rare disruptive mutations in schizophrenia[153]	Purcell et al., 2014
DX	**2009**	**Research Domain Criteria**[154] NIMH diagnostic system based on endophenotypes	Insel & Cuthbert, 2009

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