

# 전전두피질과 정신분열병

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## Prefrontal Cortex and Schizophrenia

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### ABSTRACT

With a rapid development of neuroscience, the theories related to the pathophysiology of schizophrenia have been changed a lot from a simple hyperdopaminergic one to the various complicated ones. Among these, the theories regarding prefrontal cortex(PFC) pathology as a cause of schizophrenia are gaining more recognition as the results of neuroimaging and neuropsychological tests in schizophrenia consistently report abnormalities in PFC. Therefore, we first reviewed the unique characteristics of PFC in anatomy, neurochemistry and neurophysiology to enhance an understanding of those ones. Secondly, various neurotransmitter, neurodevelopmental and neural network theories of schizophrenia introduced recently were reviewed in terms of PFC pathology.

**KEY WORDS** : Prefrontal cortex · Schizophrenia · Dopamine.

### 서 론

1950  
dopamine 가  
가 가  
dopamine 가 (Thierry 1973)  
mesocortical dopamine system  
(Thierry 1976)  
(Andreasen 1986)  
hypofrontality (Buchsbam  
Ingvar 1982 ; Farkas 1984 ; Cohen O'Leary 1992)  
Wisconsin Card Sorting Test(WCST) (Weinberg  
1986) Stroop Test(Schooler 1997)  
가 (Selemon 1995)

2 Galen , 12  
Magnus가  
(McHenry 1969)  
가 (caudal)  
(rostral)가 Ferrier(1887)  
1868 Phi -  
neas Gage가 (Andreasen 1986)  
가 (Fuster 1989) Kraepelin(1950) Ingvar 1982 ; Farkas 1984 ; Cohen O'Leary 1992)  
dementia prae -  
cox 20 Wisconsin Card Sorting Test(WCST) (Weinberg  
1986) Stroop Test(Schooler 1997)  
가 (Selemon 1995)

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clozapine

가  
dopamine

dopamine  
(Dickstein 1996)

가

가

### 본 론

#### 1. 전전두피질의 해부학적 특성

##### 1) 일반적 특성

11.5%, 3.5% 30% (Kaplan Sadock 1995a) 1.3 4.5mm (Joseph 1996) neocortex 6 layer homotypical cortex 6 layer( layer)

jections (Rose Woolsey 1948). ial cells neocortex pro - gl - (Kaplan Sadock 1995b). 60% pyramidal neurons non - pyramidal neurons amidal neurons projection neuron non - pyramidal neurons - aminobutyric acid(GABA) loca - l circuit neurons (Kaplan Sadock 1995b).

##### 2) Afferents

(corticocortical connection) neoc - (Uylings Van Eden 1990). af -

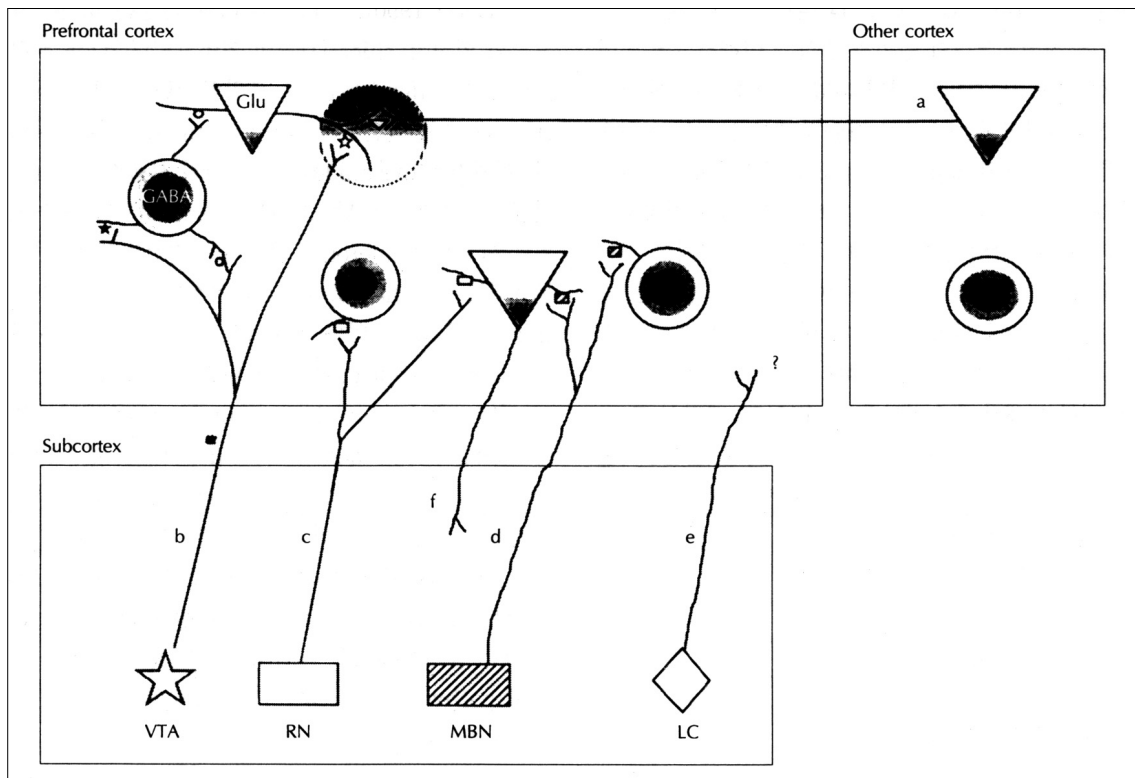
ferents pyramidal cells projections pyramidal cells pyr - amidal cells 가 af - ferents spec - ific afferents non - specific afferents Specific afferents medialis dorsalis nuc - leus thalamocortical afferents medial ventral tegmental area(VTA) (Simon 1976) mes - ocortical dopaminergic afferents가 meso - cortical afferents

(Berger 1991). Non - specific afferents noradrenergic, cholinergic, glutamatergic, serotonergic pat - hway mesocortical pathway (Kolb 1984).

##### 3) 시냅스의 구성과 수용체분포의 특성( 1).

afferents pyramidal non - pyramidal cells (pyramidal neurons dendritic spine afferents axonal ter - minals 가 ) 가 가 2 (Hutten - locher 1979) 가 2 (Hutten - locher 1979) 가 60% (pru - ning)

neuroanatomical plasticity 가 (Keshavan 1994). pyramidal cells dendritic spines de - ndritic spines gl - utamatergic dopaminergic axon terminals synaptic triad (Qian Sejnowski 1990) pyramidal cells 가 pyramidal de - ndritic spines glutamatergic axon termi - nals dopaminergic axon terminals



**Fig. 1.** Schematic diagram illustrating the principal synaptic sites and receptor location in prefrontal cortex.  
 ○ : synaptic triad comprised of dendritic spines of pyramidal cells, dopaminergic axon terminals and glutamatergic axon terminals  
 △ : glutamatergic cell, ● : GABAergic cell, VTA : ventral tegmental area, RN : raphe nucleus, MBN : magnocellular basal nucleus, LC : locus ceruleus  
 a : glutamatergic afferents, b : dopaminergic afferents, c : serotonergic afferents, d : cholinergic afferents, e : adrenergic afferents, f : glutamatergic efferents  
 △ : glutamate receptor, ● : GABA receptor, ○ : D<sub>1</sub> family receptor, ○ : D<sub>2</sub> family receptor, ○ : serotonin receptor, ○ : cholinergic receptor  
 ? : synaptic patterns remain undetermined

glutamatergic axon terminals		afferents	prefrontocortical neurons
. Synaptic triad	dopaminergic axon		basic excitatory - inhibitory
pyramidal cells	non - pyramidal ce -	functional unit	memory field
(Goldman - Rakic 1995)	pyramidal cells	Selemon 1997)	(Goldman - Rakic
non - pyramidal cells	dopaminergic neuron	inputs	afferents
GABAergic neuron	pyramidal cells	inputs	prefrontocortical ne -
pyramidal cells			urons
serotonergic afferents	non - pyramidal neurons		가
dendrites	pyramidal neurons		
(Jakab Goldman - Rakic 1996).			
dopaminergic afferents		가	가
가	Cholinergic affe -	Glutamate	NMDA
magnocellular basal nucleus(MBN)	pro -		가
pyramidal non - pyramidal neurons		(Kaplan Sadock 1995c).	Dopamine
(Gaykema 1991).		가	D <sub>1</sub>
			가 D <sub>2</sub>

(Farde 1987) D<sub>1</sub> pyra - midal neurons D<sub>2</sub> non - pyramidal neurons (Bergson 1995). Dopamine mesocortical dopaminergic axon terminal mesolimbic nigrostriatal dopaminergic axon terminal autoreceptor가 . autorece - ptor axotomy mesocortical dop - amine impulse flow dopa - mine 가가 (Bannon 1981 ; Bannon 1982) . GABA GABA<sub>A</sub> GABA<sub>B</sub> GABA<sub>B</sub> dopaminergic ter - minals dopaminergic term - inals 가 (Santiago 1993). Serotonergic 5 - HT<sub>2</sub> 가 (Pazos 1985) 5 - HT<sub>3</sub> forebrain (Kaplan Sadock 1995<sub>D</sub>). Cholinergic nicotinic 가 (Granon 1995) . Noradrenergic D<sub>1</sub> (Gold - man - Rakic 1990).

4) Efferents Efferents afferents projections (reciprocal) (Sesack 1989) efferents glutamate aspartate efferents glutamat - ergic axon terminals spiny neurons GABAnergic neurons (Freund 1984) dorsolateral prefrontal cortex loop가 efferents가 cognitive loop (Alexander 1986). efferents corticothalamic efferents가 neuronal pro - jections 가 retrosplenial areas anterior nuclei medialis dorsalis nucl - eus project thlamocortical af - ferents 가 (Beckstead RM 1979)

## 2. 전전두피질의 신경생화학 및 신경생리학적 특성

### 1) 신경생화학적 특성

(1) microdialysis glutamate 가 (Morari 1993). GABA 0.1 1 μM 10 μM 가 (Kornhuber 1984). dopamine (3 10nM) 10 가 0.3nM (deep layer) 가 (Emson Koob 1978) dopaminergic afferents 가 (Bannon Roth 1983). Serotonin 0.1nM 가 nor - epinephrine 1nM 가 ( flow rate ) 가 . (2) (3) Glutamate glutamatergic afferents gl - utamate dopaminergic terminals glutamate (AMPA/kainate ) dopamine 가 (Kalivas 1989) pyramidal neuron soma de - ndrite glutamate pyramidal cell firing 가 . GABA GABA neurones pyramidal neurons (Houser 1984) GABA py - ramidal cell soma dendrite GABA pyramidal cell firing . GA - BA neurones dopamine terminals 가 (Smiley Goldman - Rakic 1993) GABA dopamine terminals GABA<sub>B</sub> dopamine (Sa - ntiago 1993). Dopamine Dopaminergic terminals dopamine pyram - idal cell soma dendrite dopamine ( D<sub>1</sub> ) pyramidal cell (Goldman - Rakic 1989). dopam -

ine GABAergic neuron dopamine (4)  
 ( D<sub>2</sub> ) GABA glutamatergic ef -  
 가 GABA py - ferents , ,  
 ramidal cell firing 가 가 do - (Carter 1982 ; Fonnum 1981) glutamate  
 pamine pyramidal cell dopaminergic terminal do -  
 . dopamine pyramidal neuron pamine tonic stimulation (Pycock  
 dopamine 1980).  
 dopamine 가 가  
 (modulatory role) (Chiodo Berger 1986)  
 Serotonin dopamine basal output ( ) dopamine neuron 가  
 serotonergic afferents se - (Rosin 1992 ; Ro -  
 ntonin non - pyramidal neurons serotonin berts 1994).  
 target cell . non - pyr -  
 amidal neurons serotonin 5 - HT<sub>2</sub>  
 (Morilak 1993). serotonin py -  
 ramidal neurons serotonin ( 5 -  
 HT<sub>1A</sub> )(Francis 1992) target cell 가  
 (Sheldon Aghajanian 1990). serot -  
 onin - glutamate, serotonin - GABA serotonin - do - mi -  
 pamine serotonin crodialysis  
 5 - HT<sub>1B</sub> CP93,129(Lyer Bradberry 1996),  
 5 - HT<sub>2</sub> MDL 100,907(Schmidt Fadaye  
 1995), 5 - HT<sub>3</sub> 1 - phenylbiguanide neuronal pathway ,  
 (Chen 1992) dopamine 가  
 Norepinephrine  
 1 (Tanda 1992) 2 (Ta -  
 ssin 1996) dopamine 가 target cells  
 가 norepinephrine 가 imm -  
 dopamine 가 . ediate early genes(IGEs) cyclic AMP 2nd me -  
 dopamine no - ssenger target cells  
 repinephrine  
 Acetylcholine  
 acetylcholine - dopamine 2) 신경생리적 특성  
 가(Fibiger 1991 ; Levin 1990 ; (1) Mesocortical dopamine neurons  
 Tandon Greden 1989) dopamine neurons mesocortical dopamine  
 . Dopamine neurons 가  
 nicotine 가 glutamate nerve terminal  
 가 (Vidal 1994) terminal dopamine autoreceptor, dopamine cell  
 acetylcholine dopamine firing soma/dendritic dopamine auto -  
 . receptor . Terminal au -

toreceptor가 dopami -  
 nergic impulse flow do - (selective attention),  
 pamine 가 (signal detection),  
 dopamine , , ,  
 가 nigrostriatal dopamine 가 .  
 mesolimbic dopamine neurons mosocortical 가  
 dopamine neurons (Ba - (selective attention)  
 nnon 1981) soma/dendrite autorecep - (overflowing)  
 tor가 (personalization), (selective abstraction),  
 mesocortical dopamine neurons firing (overgeneralization)  
 가 (Bannon 1982)  
 . 가 .  
 mecocortical dopamine ne - working memory  
 urons (internal representation of context) . Working mem -  
 footshock stress 가 me - ory  
 socortical dopamine neurons  
 dopamine 가 가 (Thierry 1976) (Gol -  
 5-HT norepinephrine (Re - dman Selemon 1997) internal representation of context  
 inhard 1982). 가 가  
 가 가 (Cohen Servan - Schreiber 1992).  
 (Lane 1982). 가 가  
 firing  
 dopamine turnover rate가  
 mesolimbic dopamine system , nig - 가  
 rostriatal dopamine system 4 (Ba -  
 nnon 1981). dopamine me - 가  
 socortical nigrostriatal neurons soma/ dopamine dopamine 가  
 dendritic terminal autoreceptor dopamine  
 가 가 hypodopaminergic state가 working memory int -  
 mesocortical neurons ernal representation of cortex  
 (Demerest Moore 1979). 가 . 가  
 dopamine 가가 D<sub>1</sub>  
 30% (Bannon 1981) (Sawagu -  
 가 chi Goldman - Rakic 1994) (Carter  
 dopamine Pycock 1980 ; Sawaguchi 1990)  
 mesolimbic nigrostriatal neurons NMDA ketamine Wisconsin  
 dopamine 가가 Card Sorting Test(WCST)  
 (tolerance) mesocortical neurons (Krystal 1994) glutamate  
 가  
 ( 30%) 가 . glutamatergic dopami -  
 (2) nergic neurons output 가

3. 전전두피질과 관련된 정신분열병의 발생가설들

가설 1: 전전두피질에서 glutamate 가 dopaminergic terminal dopamine 가 (Costall Naylor 1975 ; Ridley 1988). dopamine tonic release(glutamate dopaminergic terminal dopamine 가 ) dopamine phasic release(cell body firing dopaminergic terminal dopamine 가 ) ( dopamine up - regulation) (Grace 1991).

1) 신경전달물질가설

(1) Dopamine 가 Uncoupling hypothesis of D<sub>1</sub> receptor dopamine pyramidal cell firing (nucleus accumbens) corticofugal corticostriatal glutamatergic neuron terminal glutamate 가 . Glutamate dopaminergic terminal dopamine (locomotor suppression) (Bradbury 1984 ; Willns 1991) dopamine mesolimbic nigrostriatal dopaminergic neuronal firing 가 dopamine 가 dopamine (Keller 1983) dopaminergic terminal uncoupling D<sub>1</sub> unco - pling D<sub>2</sub> D<sub>1</sub> uncoupling dopamine dopamine hypodopaminergic state 가 dopamine 가 (Breier 1991 ; Jones 1988) dopamine 가 (Robbins 1990)

가설 2: dopamine - serotonin 가 (Carlsson 1995). Dopamine - serotonin 가 (Meltzer 1989) 가 clozapine 5 - HT<sub>2</sub> dopamine dopamine - serotonin 가 cloz - apine (Yamamoto Cooperman 1994) dopamine 가 (You - ngren 1994) dopamine 가 D<sub>2</sub> D<sub>1</sub> clozapine D<sub>1</sub> D<sub>2</sub> 5 - HT<sub>2</sub> (Ki nM) : clozapine D<sub>1</sub> 85 ± 0.7, D<sub>2</sub> 125 ± 20, 5 - HT<sub>2A</sub> 12 ± 3, haloperdol : D<sub>1</sub> 25 ± 7, D<sub>2</sub> 1 ± 0.04, 5 - HT<sub>2A</sub> 78 ± 22(Byma - ster 1996) - clozapine D<sub>1</sub> 5 - HT<sub>2A</sub> dopamine 가 dopamine 가 dopamine 가





naptic pruning (Weinberger 1987). 가 (2) Computer simulation model (sequential mode) (parallel) 가 가  
 pruning 가 (content) 가  
 synaptic hyperpruning (Keshavan 1994) hyperpruning 가 (content - addressable memory system) Hopfield network(Hopfield 1982) (3) Hoffman (Hoffman Dobscha 1989) Hoffman Hopfield network (un-  
 minal dopamine axon terminals) 가 (cortical pruning 80% "loose associations" "parasitic foci" Loose association (functional fragmentation) pruning 가 parasitic foci unit unit 가  
 pruning 가 dopamine 가 가 가 parasitic foci가 가  
 estrogen axon (Naftolin 1990) 가 cortical hyperpruning 가  
 3) 신경망가설 (4) Cohen (Cohen Servan - Schreiber 1993) 가 dopamine 가 (Stroop task, continuous performance test, lexical disambiguation task) units unit do-  
 (1) Filter model(Broadbent 1971 ; Frith 1979 ; Carlsson 1994) 가 hypofrontality (hypodopaminergic state )(Weinberger Bernan 1988) 가 가 가  
 Frith frontostriatum Broadbent Carlsson 가 dopamine

가  
가  
가 hyperpruning dopamine  
dopamine  
ffman hyperpruning dopamine  
dopamine 가  
(Cohen )  
가 dopamine  
dopamine

## 결 론

가 dopamine  
(Chua McKenna 1995)  
가  
가

중심 단어 :

## 참고문헌

Alexander GE, DeLong M, Strick PE(1986) : Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Rev Neurosci* 9 : 357-381  
Andreasen NC, Nasrallah HA, Dunn V, Olson Sc, Groove WM, Herhard JC, Coffman JA, Crossett JHW(1986) : Structural abnormalities in the frontal systems of schizophrenia. *Arch Gen Psychiatry* 43 : 136-144  
Bannon MJ, Bunney EB, Roth RH(1981) : Mesocortical dopamine neurons : rapid transmitter turnover compared to other brain catecholamine system. *Brain Res* 218 : 376-382

Bannon MJ, Chiodo LA, Roth RH, Bunney BS(1982) : Mesocortical dopamine neurons : electrophysiological and biochemical evidence for the absence of autoreceptors in a subpopulation. *Soc Neurosci Abstr* 8 : 480  
Bannon MJ, Michaud RL, Roth RH(1981) : Mesocortical dopamine neurons : lack of autoreceptors modulating dopamine synthesis. *Mol Pharmacol* 19 : 270-275  
Bannon MJ, Reinhard JF, Bunney EB, Roth RH(1982) : Unique response to antipsychotic drugs is due to the absence of terminal autoreceptors in mesocortical dopamine neurons. *Nature* 296 : 444-446  
Bannon MJ, Roth RH(1983) : Pharmacology of mesocortical dopamine neurons. *Pharmacol Rev* 35 (1) : 53-68  
Beckstead RM(1979) : An autoradiographic examination of corticocortical and subcortical projections of the mediodorsal projection cortex in the rat. *J Comp Neurol* 184 : 43-62  
Berger B, Gaspar P, Verney C(1991) : Dopaminergic innervation of the cerebral cortex : unexpected differences between rodents and primates. *Trends Neurosci* 14 : 21-27  
Bergson C, Mrzizjak L, Smiley JF, Pappy M, Levenson R, Goldman-Rakic PS(1995) : Regional, cellular, and subcellular variations in the distribution of D<sub>1</sub> and D<sub>5</sub> dopamine receptors in primate brain. *J Neurosci* 15 : 7821-7837  
Bourgeois JP, Goldman-Rakic PS, Rakic P(1994) : Synaptogenesis in the prefrontal cortex of rhesus monkeys. *Cereb Cortex* 4 : 78-96  
Bradbury AJ, Costall B, Naylor RJ(1984) : Inhibition and facilitation of motor responding of the mouse by actions of dopamine agonists in the forebrain. *Neuropsychopharmacology* 23 : 1025-1031  
Breier A, Wolkowitz OM, Pickar D(1991) : Stress and schizophrenia. In : *Schizophrenia Research*. Ed by Schultz Sc, Tamminga CA, New York, Raven Press, pp141-152  
Broadbent DE(1971) : *Decision and stress*. San Diego, CA : Academic Press  
Buchsbaum MS, Ingvar DH(1982) : New visions of the schizophrenic brain : Regional difference in electrophysiology, blood flow, and cerebral glucose use. New York, Oxford University Press, pp235-252  
Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore Na, Tye NC, Seeman P, Wong DT(1996) : Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 14 : 87-96  
Carlsson A(1994) : Search for the neuronal circuitries and neurotransmitters involved in positive and negative schizophrenic symptomatology. *Fidia Research Foundation Neuroscience Award Lectures, Vol 5*, New York, Raven Press  
Carlsson A(1995) : The dopamine theory revisited. In : *Schizophrenia*. Ed by Hirsch SR, Weinberger DR, Oxford, Blackwell Science, pp379-400  
Carlsson M, Carlsson A(1990) : System within the basal ganglia : implications for schizophrenia and parkinson's disease. *Trends Neuro Sci* 13 : 272-276  
Carter CJ(1982) : Topographical distribution of possible glutamatergic pathways from the frontal cortex to the striatum and substantia nigra in rats. *Neuropharmacology* 21 : 379-383  
Carter CJ, Pycock CJ(1980) : Behavioral and biochemical effects of dopamine and noradrenaline depletion within the medial pr-

- frontal cortex of the rat. *Brain Res* 192 : 163-176
- Chen JP, Pardes W, van Praag HM, Lowinson JH, Gardner EL (1992)** : Presynaptic dopamine release enhanced by 5-HT<sub>3</sub> receptor activation in medial prefrontal cortex of freely moving rats. *Synapse* 10 : 264-256
- Chiodo LA, Berger TW(1986)** : Interactions between dopamine and amino acid-induced excitation and inhibition in the striatum. *Brain Res* 375 : 198-203
- Chua SE, McKenna PJ(1995)** : Schizophrenia-a brain disease? A critical review of structural and cerebral abnormality in the disorder. *Br J Psychiatry* 166 : 563-582
- Cohen G, O'Leary DS(1992)** : Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. *Arch Gen Psychiatry* 49 : 943-958
- Cohen JD, Servan-Schreiber D(1992)** : Context, cortex, and dopamine : A connectionist approach to behavior and biology in schizophrenia. *Psychol Rve* 99 (1) : 45-77
- Cohen JD, Servan-Schreiber D(1993)** : A theory of dopamine function and its role in cognitive deficits in schizophrenia. *Schizophrenia Bull* 19 (1) : 85-104
- Costall B, Naylor RJ(1975)** : The behavioral effects of dopamine applied intracerebrally to areas of the mesolimbic system. *Eur J Pharmacol* 32 : 87-92
- Demerest KT, Moore KE(1979)** : Comparison of dopamine synthesis regulation in the terminals of nigrostriatal, mesolimbic, tuberoinfundibular and tuberohypophysial neurons. *J Neural Transm* 46 : 263-277
- Dickstein LJ, Riba MB, Oldham JM(1996)** : Review of psychiatry. Vol 15, Washington, American Psychiatric Press, pp367
- Emson PC, Koob GF(1978)** : The origin and distribution of dopamine-containing afferents to the rat frontal cortex. *Brain Res* 142 : 249-267
- Farde L, Halldin C, Stone-Elander S, Sedvall G(1987)** : PET analysis of human dopamine receptor subtypes using 11C-ScH 23390 and 11C-raclopride. *Psychopharmacology* 92 : 278-284
- Farkas T, Wolf AP, Jaeger J, Brodie JD, Christman DR, Fowler JS(1984)** : Regional brain glucose metabolism in chronic schizophrenia. *Arch Gen Psychiatry* 41 : 293-300
- Feinberg I(1982)** : Schizophrenia : caused by a fault in programmed synaptic elimination during adolescence? *J Psych Res* 17 : 319-330
- Ferrier D(1887)** : Functions of the brain. 2nd ed, London, Smith, Elder
- Fibiger HC(1991)** : Dopaminergic-cholinergic interactions in the striatum. *Jpn J Psychiatry Neurol* 45 (2) : 512
- Fonnum F, Storm-Mathison J, Divac I(1981)** : Biochemical evidence for glutamate as neurotransmitter in corticostriatal and corticothalamic fibers in rat brain. *Neuroscience* 6 : 863-873
- Francis PT, Pangalos MN, Pearson RCA, Middlemiss DN, Strattmann GC, Bowen DM(1992)** : 5-hydroxytryptamine 1a but not 5-hydroxytryptamine 2 receptors are enriched on neocortical pyramidal neurons destroyed by intrastriatal volkensin. *J Pharmacol Exp Ther* 261 : 1273-1281
- Freund TF, Poweill JF, Smith ADT(1984)** : *Neuroscience* 13 : 1189-1215
- Frith CD(1979)** : Consciousness, information processing and schizophrenia. *Br J Psychiatry* 134 : 225-235
- Fuster JM(1989)** : *The prefrontal cortex*. New York, Raven Press
- Gaykema RPA, Gaal G, Traber J, Hersh LB, Luiten PGM(1991)** : The basal forebrain cholinergic system : efferent and afferent connectivity and long-term effects of lesions. *Acta Psychiatr Scand* 366 (suppl) : 14-26
- Goldman-Rakic PS, Leranath C, Williams SM, Mons N, Geffard M (1989)** : Dopamine synaptic complex with pyramidal neurons in primate cerebral cortex. *Proc Natl Acad Sci* 86 : 9015-9019
- Goldman-Rakic PS, Lidown MS, Gallager DW(1990)** : Overlap of dopaminergic, adrenergic, and serotonergic receptors and complementarity of their subtypes in primate prefrontal cortex. *J Neurosci* 10 : 2125-2138
- Goldman-Rakic PS, Selemon LD(1997)** : Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophrenia Bull* 23 (3) : 437-458
- Grace AA(1991)** : Phasic versus tonic dopamine release and the modulation of dopamine system responsivity : a hypothesis for the etiology of schizophrenia. *Neuroscience* 41 (1) : 1-24
- Granon S, Poucet B, Thinus-Blanc C, Changeux JP, Vidal C (1995)** : Nicotinic and muscarinic receptors in the rat prefrontal cortex : differential roles in working memory, response selection and effortful processing. *Psychopharmacology* 119 : 139-144
- Hoffman RE, Dobscha SK(1989)** : Cortical pruning and the development of schizophrenial a computer model. *Schizophrenia Bull* 15 (3) : 477-490
- Hopfield JJ(1982)** : Neural networks and physical systems with emergent collective computational abilities. *Proc Natl Acad Sci* 79 : 2554-2558
- Houser CR, Vaughn JE, Hendry SCH, Jones EG, Peters A(1984)** : Functional properties of cortical cells. Vol 2, New York, Plenum Press, pp63-90
- Huttenlochei PR(1979)** : Synaptic density in human frontal cortex : developmental changes and effects of aging. *Brain Res* 163 : 195-205
- Iyer RN, Bradberry CW(1996)** : Serotonin-mediated increase in prefrontal cortex dopamine release : pharmacological characterization. *J Pharmacol Exp Ther* 277 : 40-47
- Jakab RL, Goldman-Rakic PS(1996)** : Presynaptic and postsynaptic subcellular localization of substance P receptor immunoreactivity in the neostriatum of the rat and rhesus monkey. *J Comp Neurol* 369 : 125-136
- Jedema HP, Moghaddam B(1994)** : Glutamatergic control of dopamine release during stress in the rat prefrontal cortex. *J Neurochem* 63 : 785-788
- Jones GH, Hrnandez TD, Marsden CA, Robbins TW(1988)** : Enhanced striatal response to d-adphetamine as revealed by intracerebral dialysis following social isolation in rats. *Br J pharmacol* 94 : 349P
- Joseph R(1996)** : *Neuropsychiatry, neuropsychology, and clinical neuroscience*. 2nd ed, Baltimore, Williams & Wilkins, pp395
- Kalivas PW, Duffy P, Barrow J(1989)** : Regulation of the mesocorticolimbic dopamine system by glutaminc acid receptor subtypes. *J Pharmacol Exp Ther* 251 : 378-387
- Kaplan HI, Sadock BJ(1995a)** : *Comprehensive textbook of psychiatry*. 6th ed, Baltimore, Williams & Wilkins, pp6
- Kaplan HI, Sadock BJ(1995b)** : *Comprehensive textbook of psych-*

- iatry. 6th ed, Baltimore, Williams & Wilkins, pp13
- Kaplan HI, Sadock BJ(1995c)** : *Comprehensive textbook of psychiatry. 6th ed, Baltimore, Williams & Wilkins, pp34*
- Keller RW, Stricker EM, Zigmond MJ(1983)** : *Environmental stimuli but not homeostatic challenges produce apparent increases in dopaminergic activity in the striatum : an analysis by in vivo voltametry. Brain Res 279 : 159-170*
- Keshavan MS, Anderson S, Pettegrew JW(1994)** : *Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? : The Feinberg hypothesis revisited. J Psychiat Res 28 (3) : 239-265*
- Kolb B(1984)** : *Functions of the frontal cortex of the rat : A cooperative review. Brain Res Rev 8 : 65-98*
- Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmüller B(1980)** : *Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neurosci Lett 20 : 379-382*
- Kornhuber J, Kim JS, Kornhuber ME, Kornhuber HH(1984)** : *Chronic haloperidol administration enhances the  $\gamma$ -aminobutyric acid level in the rat striatum without altering the glutamate level. Eur Neurol 23 : 269-273*
- Kraepelin E(1950)** : *Dementia praecox and paraphrenia. New York, International University Press Krystal JH, Karper LP, Seibyl JP, et al (1994) : Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Arch Gen Psychiatry 51 : 199-214*
- Lane JD, Sands MP, Cherek DR, Smith JE(1982)** : *Biogenic monoamine turnover in discrete rat brain regions is correlated with conditioned emotional response and its conditioning history. Brain Res 240 : 95-108*
- Levin ED, McGurk SR, Rose JE, Butcher LL(1990)** : *Cholinergic-dopaminergic interactions in cognitive performance. Behav Neural Biol 54 (3) : 271-299*
- Lim KO, Harris D, Beal M, Hoff AL, Minn K, Csernansky JG, Faustman WO, Marsh L, Sullivan EV, Pfefferbaum A(1995)** : *Gray matter deficits in young onset schizophrenia are independent of age at onset. Biol Psychiatry 40 : 4-13*
- Lynch MR(1992)** : *Schizophrenia and D<sub>1</sub> receptor : focus on negative symptoms. Prog Neuro-Psychopharmacol & Biol Psychiat 16 : 797-832*
- McHenry LC(1969)** : *Garrison's history of neurology. Charles C. Thomas, Springfield, IL*
- Meltzer HY(1989)** : *Clinical studies on the mechanism of action of clozapine : The dopamine-serotonin hypothesis of schizophrenia. Psychopharmacology 99 (suppl) : S18-S27*
- Morari M, O'Connor WT, Ungerstedt U, Fuxe K(1993)** : *N-methyl-D-aspartic acid differentially regulates extracellular dopamine, GABA, and glutamate levels in the dorsolateral neostriatum of the halothane-anesthetized rat : an in vivo microdialysis study. J neurochem 60 : 1884-1893*
- Morilak DA, Garlow SK, Ciaranello RD(1993)** : *Immunocytochemical localization and description of neurons expressing serotonin 2 receptors in the rat brain. Neuroscience 54 : 701-717*
- Naftolin F, Garcia-Segura LM, Keefe D(1990)** : *Estrogen effects on the synaptology and neural membranes of the rat hypothalamic arcuate nucleus. Biol Reprod 42 : 21-28*
- Pazos A, Cortes R, Palacios JM(1985)** : *Quantitative autoradiographic mapping of serotonin receptors in the rat brain. Brain Res 346 : 231-249*
- Pycock CJ, Kerwin RW, Carter CJ(1980)** : *Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature 286 : 74-77*
- Qian N, Sejnowski T(1990)** : *When is an inhibitory synapse effective? Proc Natl Acad Sci 87 : 8145-8149*
- Reinhard JF, Bannon MJ, Roth RH(1982)** : *Acceleration by stress of dopamine synthesis and metabolism in prefrontal cortex : antagonism by diazepam. Naunyn-Schmiedeberg's Arch Pharmacol 318 : 374-477*
- Ridley RM, Baker HF, Frith CD, Dowdy J, Crow TJ(1988)** : *Stereotyped responding on a two-choice guessing task by marmosets and humans treated with amphetamine. Psychopharmacology 95 : 560-564*
- Robbins TW(1990)** : *The case for frontostriatal dysfunction in schizophrenia. Schizophrenia Bull 16 (3) : 391-402*
- Roberts AC, De Salvia MA, Wilkinson LS, et al(1994)** : *6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sorting Test : possible interactions with subcortical dopamine. J Neurosci 14 : 2531-2544*
- Rose M, Woolsey C(1948)** : *The orbitofrontal cortex and its connections with the mediodorsal nucleus in the rabbit, sheep and cat. Res Publ Assoc Res Nerv Ment Dis 27 : 210-232*
- Rosin DL, Clark WA, Goldstein M, et al(1992)** : *Effects of 6-hydroxydopamine lesions of the prefrontal cortex on tyrosine hydroxylase activity in mesolimbic and nigrostriatal dopamine systems. Neuroscience 48 : 831-839*
- Santiago M, Machado A, Cano J(1993)** : *In vivo release of dopamine from rat striatum, substantia nigra and prefrontal cortex : differential modulation by baclofen. Br J Pharmacol 109 : 814-818*
- Sawaguchi T, Goldman-Rakic PS(1994)** : *The role of D<sub>1</sub>-dopamine receptor in working memory : local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. J Neurophysiol 71 : 515-528*
- Sawaguchi T, Matsumura M, Kubota K(1990)** : *Effects of dopamine antagonists on neuronal activity related to a delayed response task in monkey. J Neurophysiol 63 : 1401-1412*
- Schmidt CJ, Fadaye GM(1995)** : *The selective 5-HT 2A receptor antagonist, MDL 100,907, increases dopamine efflux in the prefrontal cortex of the rat. Eur J Pharmacol 273 : 273-279*
- Schooler C, Neumann E, Caplan LJ, Roberts BR(1997)** : *A time course analysis of Stroop interference and facilitation : Comparing normal individuals and individuals with schizophrenia. J Exp Psychol 126 : 19-36*
- Selemon LD, Rajkowska G, Goldman-Rakic PS(1995)** : *Abnormally high neuronal density in two widespread areas of the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry 52 : 805-818*
- Sesack SR, Bunney BS(1989)** : *Pharmacological characterization of the receptor mediating electrophysiological responses to dopamine in the rat medial prefrontal cortex : A microiontophoretic study. J Pharmacol Exp Ther 248 : 1323-1333*
- Sesack SR, Snyder CL, Lewis DA(1995)** : *Axon terminals immunolabeled for dopamine or tyrosine hydroxylase synapse on GABA-immunoreactive dendrites in rat and monkey cortex. J Comp Neurol 363 : 264-280*

- Sheldon PW, Aghajanian GK(1990)** : Serotonin (5-HT) induces IPSPs in pyramidal layer cells of rat pyriform cortex. Evidence for the involvement of a 5-HT<sub>2</sub>-activated interneuron. *Brain Res* 506 : 62-69
- Simon H, LeMoal M, Galey D, Cardo B(1976)** : Silver impregnation of dopaminergic system after radiofrequency and 6-OHDA lesions of the rat ventral tegmentum. *Brain Res* 115 : 215-231
- Smiley JF, Goldman-Rakic PS(1993)** : Heterogeneous targets of dopamine synapses in monkey prefrontal cortex demonstrated by serial electron microscopy : a laminar analysis using the silver-enhanced diaminobenzidine sulfide (SEDS) immunolabeling technique. *Cerebral Cortex* 3 (3) : 223-238
- Snell LD, Johnson KM(1986)** : Antagonism of N-methyl-D-aspartate-induced transmitter release in the rat striatum by phencyclidine-like drugs and its relationship to turning behavior. *J Pharmacol Exp Ther* 235 : 50-57
- Tanda G, Carboni E, Frau R, Chiara GD(1994)** : Increase of extracellular dopamine in the prefrontal cortex : A trait of drugs with antidepressant potential? *Psychopharmacology* 115 : 285-288
- Tandon R, Greden JF(1989)** : Cholinergic hyperactivity and negative schizophrenia symptoms. A model of cholinergic / dopaminergic interactions in schizophrenia. *Arch Gen Psychiatry* 46 (8) : 745-753
- Tassin JP(1996)** : Mianserin markedly and selectively increases extracellular dopamine in the prefrontal cortex as compared to the nucleus accumbens of the rat. *Psychopharmacology* 123 (2) : 127-130
- Thierry AM, Blanc G, Sobel A, et al(1973)** : Dopaminergic terminals in the rat cortex. *Science* 182 : 499-501
- Thierry AM, Tassin JP, Blanc G, et al(1976)** : Selective activation of the mesocortical dopamine system by stress. *Nature* 263 : 242-244
- Uylings HBM, Van Eden CG(1990)** : Qualitative and quantitative comparison of the prefrontal cortex in the rat and in primates, including humans in the prefrontal cortex : its structure, function, and pathology. Amsterdam, Elsevier, pp31-62
- VanKammen DP(1977)** : Gamma-aminobutyric acid (GABA) and the dopamine hypothesis of schizophrenia. *Am J Psychiatry* 134 : 138-143
- VanKammen DP, Gelernter J(1987)** : Biochemical instability in schizophrenia. II. The serotonin and gamma-aminobutyric acid systems. In : Meltzer HY (ed) *Psychopharmacology : the third generation of progress*. New York, Raven Press, pp753-758
- Vidal C(1994)** : Nicotinic potentiation of glutamatergic synapses in the prefrontal cortex : new insight into analysis of the role of nicotinic receptors in cognitive functions. *Drug Dev Res* 31 : 120-126
- Weinberger DR(1987)** : Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44 : 660-669
- Weinberg DR, Berman KF(1988)** : Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophrenia Bull* 14 (2) : 157-168
- Weinberg DR, Berman KF, Zec RF(1996)** : Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia : I. Regional cerebral blood flow (rCBF) evidence. *Arch Gen Psychiatry* 43 : 114-125
- Willins DL, Wallace LJ, Gerald NC, Uretsky NJ(1991)** : AMPA / Kainate glutamate receptor antagonists in the nucleus accumbens selectively decrease the hypermotility response to amphetamine. *Soc Neurosci Abs* 17 : 1431
- Yamamoto BK, Cooperman MA(1994)** : Differential effects of chronic antipsychotic drug treatment on extracellular glutamate and dopamine concentrations. *J Neurosci* 14 : 4159-4166
- Youngren KD, Moghaddam B, Bunney BS, et al(1994)** : Preferential activation of dopamine overflow in prefrontal cortex produced by chronic clozapine treatment. *Neurosci Lett* 165 : 41-44