日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会．イブニングセミナー6、平成20年10月2日．東京都．

9. 橋本謙二（2008）統合失調症の認知機能障害と治療薬に関する研究．第8回精神疾患と認知機能研究会．平成20年11月8日．東京都．
10. Hashimoto, K. (2009) Recent findings on sigma-1 receptors and fluvoxamine. In Symposium "Second Expanding Clinical Knowledge on Fluvoxamine. Florence, Italy, March 31, 2009.
11. 石川雅智、石井賢二、木村裕一、坂田宗之、織田圭一、石渡喜一、伊豫雅臣、橋本謙二（2008）ドネペジルによるシグマ-1受容体の占拠：[^{11}C]SA4503-PETを用いて．第12回神経科学領域における分子モニタリングシンポジウム．2008年4月19日、浜松市．
12. 金原信久、清水栄司、内田佳孝、橋本謙二、伊豫雅臣（2008）統合失調症患者の脳血流変化と言語流暢性機能：病初期と慢性期を比較する．第12回神経科学領域における分子モニタリングシンポジウム．2008年4月19日、浜松市．
13. 萩原裕子、藤田有子、石間環、伊豫雅臣、橋本謙二（2007）フェインサイクリジン投与による認知機能障害に及ぼす非定型抗精神病薬ペロスピロンの効果．第13回日本行動薬理研究会.2008年6月6日、千葉市．
14. 金原信久、清水栄司、大掛真太郎、藤田有子、橋本謙二、伊豫雅臣（2008）MK-801によるプレパルス抑制障害に対するNMDA受容体グリシンサイトアゴニストの改善作用．第13回日本行動薬理研究会．2008年6月6日、千葉市．
15. 趙英らん、宮一志、橋本謙二、森　寿（2008）脳内D－セリンの機能解析．第31回日本神経科学会大会．2008年7月10日、東京都．
16. 滝沢　龍、橋本謙二、栃木　衛、川久保友紀、丸茂浩平、佐々木　司、福田正人、笠井清登（2008）統合失調症におけるシグマ-1受容体遺伝子多型と前頭葉機能との関連：多チャンネルNIRS研究．第18回日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会．平成20年10月1日．東京都．
17. 井上秀之、山末英典、橋本謙二、栃木　衛、菅　心、阿部　修、山田晴耕、青木茂樹、佐々木　司、笠井清登（2008）シグマ-1受容体遺伝子多型が海馬・扁桃体体積に与える影響．第18回日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会．平成20年10月1日．東京都．
18. 伊豫雅臣、白山幸彦、渡邊博幸、藤崎美久、宮武良輔、深見悟郎、椎名明大、中里道子、白石哲也、尾上毅、橋本謙二（2008）シグマ-1受容体アゴニストとしてのフルボキサミン投与により認知機能障害が改善した統合失調症患者の一例.第18回日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会．平成20年10月1日．東京都．
19. 石間　環、西村智子、伊豫雅臣、橋本謙二（2008）PC12細胞におけるNGF誘発神経突起促進作用に及ぼすフルボキサミンの増強作用．第18回日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会．平成20年10月1日．東京都．
20. 藤田有子、石間　環、河野眞美、萩原裕子、伊豫雅臣、橋本謙二（2008）フェンサイクリジン投与による認知機能障害に

及ぼすフルボキサミンの改善作用：シグマ-1受容体の関与. 第18回日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会. 平成20年10月1日. 東京都.

21. 石川雅智、石渡喜一、石井賢二、木村裕一、坂田宗之、長縄美香、織田圭一、伊豫雅臣、橋本謙二（2008）フルボキサミン単回投与によるヒト脳内シグマ-1受容体占拠について：[^{11}C]SA4503—ポジトロンCT(PET)撮影を用いて. 第18回日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会. 平成20年10月2日. 東京都.

22. Watanabe, A., Toyota, T., Owada, Y., Hayashi, T., Iwayama, Y., Matsumata, M., Ishitsuka, Y., Maekawa, M., Ohnishi, T., Yamada, K., Hashimoto, K., Osumi, N., and Yoshikawa, T. (2008) プレパルスインヒビションのQTL解析による責任遺伝子の同定.第18回日本臨床精神神経薬理学会・第38回日本神経精神薬理学会合同学会. 平成20年10月2日. 東京都.

H. 知的財産権の出願・登録状況

なし

Ⅲ. 業 績 一 覧

研究成果の刊行に関する一覧表

書　籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
福田正人 亀山正樹	脳画像検査	山内俊雄・ 岡崎祐士・ 神庭重信・ 小山司・ 武田雅俊	精神科専門医のためのプラクティカル精神医学	中山書店	東京	印刷中	
福田正人			精神疾患とNIRS - 光トポグラフィー検査による脳機能イメージング	中山書店	東京	印刷中	
福田正人 青山義之 武井雄一 成田耕介	NIRSの神経生理学的基礎	福田正人	精神疾患とNIRS - 光トポグラフィー検査による脳機能イメージング	中山書店	東京	印刷中	
福田正人 須田真史 亀山正樹 上原徹	精神疾患におけるNIRSの意義	福田正人	精神疾患とNIRS - 光トポグラフィー検査による脳機能イメージング	中山書店	東京	印刷中	
心の健康に光トポグラフィー検査を応用する会, 福田正人 三國雅彦	NIRS検査法標準化の試み	福田正人	精神疾患とNIRS - 光トポグラフィー検査による脳機能イメージング	中山書店	東京	印刷中	
滝沢龍，福田正人，心の健康に光トポグラフィー検査を応用する会	多数データ・個別データの解析	福田正人	精神疾患とNIRS - 光トポグラフィー検査による脳機能イメージング	中山書店	東京	印刷中	
福田正人，心の健康に光トポグラフィー検査を応用する会	NIRS検査による精神疾患の診断	福田正人	精神疾患と脳画像	中山書店	東京	2008	227-241
福田正人			専門医のための精神科臨床リュミエール 『精神疾患と脳画像』	中山書店	東京	2008	

滝沢龍、 川久保友紀 桑原斉 笠井清登	統合失調症・自閉症の前頭葉機能障害とNIRSの臨床応用	福田正人	精神疾患とNIRS	中山書店	東京	2009	In press
西村幸香 滝沢龍 笠井清登	NIRSデータの再現性	福田正人	精神疾患とNIRS	中山書店	東京	2009	In press
西村幸香 横山知加 谷井久志 笠井清登 貝谷久宣 岡崎祐士	パニック障害・不安障害	福田正人	精神疾患とNIRS	中山書店	東京	2009	In press
大西隆	脳画像検査の実際：fMRI	平安良雄 笠井清登	精神疾患の脳画像解析・診断学	南山堂	東京	2008	37-44
大西隆	脳構造と遺伝子	福田正人	専門医のための精神科臨床リュミエール2 精神疾患と脳画像	中山書店	東京	2008	183-190
根本清貴	脳画像検査の実際：sMRI-VBM	平安良雄 笠井清登	精神疾患の脳画像解析・診断学	南山堂	東京	2008	12-18
根本清貴	Alzheimer病のSPECT診断	福田正人	専門医のための精神科臨床リュミエール2 精神疾患と脳画像	中山書店	東京	2008	216-226
Yamasue H, Kato N	Sexually dimorphism and social brain circuit: its implication to Autism	本間　生夫 塩田　清二	Transmitters and Modulators in Health and Disease.	Springer		in press	
井上秀之 山末英典 ほか	統合失調症の脳構造	福田正人	精神疾患と脳画像	中山書店		2008	58-69.
山末英典 ほか	PTSD	福田正人	精神疾患と脳画像	中山書店		2008	89-99
山末英典	自閉症	平安良雄 笠井清登	精神疾患の脳画像解析・診断学	南山堂		2008	109-110

雑　誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takizawa R, Hashimoto K, Tochigi M, Kawakubo Y, Marumo K, Sasaki T, Fukuda M, Kasai K	Association between sigma-1 receptor gene polymorphism and prefrontal hemodynamic response induced by cognitive activation in schizophrenia.	*Prog Neuropsychopharmacol Biol Psychiatry*			in press
Nishida A, Sasaki T, Harada S, Fukuda M, Masui K, Nishimura Y, Ikebuchi E, Okazaki Y	Risk of developing schizophrenia among Japanese high-risk offspring of affected parent: outcome of a twenty-four-year follow up.	*Psychiat Clin Neurosci*	63:	88-93.	2009
Suda M, Fukuda M, Sato T, Iwata S, Song M, Kameyama M, Mikuni M	Subjective feeling of psychological fatigue is related to decreased reactivity in ventrolateral prefrontal cortex..	*Brain Res*:	1252	152-160	2009
Aoyama Y, Hanaoka N, Kameyama M, Suda M, Sato T, Song M, Fukuda M, Mikuni M	Stimulus intensity dependence of cerebral blood volume changes in left frontal lobe by low-frequency rTMS to right frontal lobe: a near-infrared spectroscopy study	*Neurosci Res*:	63	47-51.	2009
Takei Y, Kumano S, Hattori S, Uehara T, Kawakubo Y, Kasai K, Fukuda M, Mikuni M	Preattentive dysfunction in major depression: magnetoencephalography study using auditory mismatch negativity	*Psychophysiology*:.	46	52-61	2009
Matsubayashi J, Kawakubo Y, Suga M, Takei Y, Kumano S, Fukuda M, Kenji I, Yumoto M, Kasai K	The influence of gender and personality traits on individual difference in auditory mismatch: a magnetoencephalographic (MMNm) study.	*Brain Res*	1236	159-165	2008
Takizawa R, Kasai K, Kawakubo Y, Marumo M, Kawasaki S, Yamasue H, Fukuda M	(Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study.	*Schizophr Res*	99	250-262	2008
Suda M, Sato T, Kameyama M, Ito M, Suto T, Yamagishi Y, Uehara T, Fukuda M, Mikuni M	Decreased cortical reactivity underlies subjective daytime light sleepiness in healthy subjects: a multichannel near-infrared spectroscopy study.	*Neurosci Res*	60	319-326	2008

福田正人	神経生理から見た統合失調症の病態生理	脳 21			印刷中
滝沢龍，笠井清登，川久保友紀，丸茂浩平，川崎真護，山末英典，福田正人	統合失調症における前頭極と機能障害の関連ー多チャンネル近赤外線スペクトロスコピー（NIRS）研究	脳と精神の医学	19	219-227	2008
福田正人，須田真史，青山義之，武井雄一，佐藤利正，亀山正樹，成田耕介，上原徹，三國雅彦	NIRSの神経生理学的基礎	臨床精神医学	37	1283-1294	2008
福田正人	統合失調症の臨床診断と疾患概念	精神科診断学	1	28-38	2008
Sumiyoshi T., Kawasaki Y., Suzuki M., Higuchi Y., Nishiyama S., Kurachi M.	Neurocognitive assessment and pharmacotherapy towards prevention of schizophrenia: What can we learn from first episode psychosis?	*Clinical Psychopharmacology and Neuroscience*	6(2)	57-64	2008
Sumiyoshi T.	A possible dose-side effect relationship of antipsychotics: Relevance to cognitive function in schizophrenia	*Clinical Expert Review of Clinical Pharmacology*	1(6)	791-812	2008
兼田康宏、住吉太幹、中込和幸、沼田周助、田中恒彦、上岡義典、大森哲郎、Keefe R.S.E	統合失調症認知機能簡易評価尺度日本語版(BACS-J)	精神医学	50(9)	913-17	2008
Marumo K, Takizawa R, Kawakubo Y, Onitsuka T, Kasai K	Gender difference in right lateral prefrontal hemodynamic response while viewing fearful faces: A multi-channel near-infrared spectroscopy study	Neurosci Res	63(2)	89-94	2009
Takizawa R, Hashimoto K, Tochigi M, Kawakubo Y, Marumo K, Sasaki T, Fukuda M, Kasai K	Association between sigma-1 receptor gene polymorphism and prefrontal hemodynamic response induced by cognitive activation in schizophrenia	Prog Neuropsychopharmacol Biol Psychiatry	In press		2009

Takizawa R, Kasai K, Kawakubo Y, Marumo K, Kawasaki S, Yamasue H, Fukuda M	Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study	Schizophr Res	99	250-262	2008
木納賢、滝沢龍、丸茂浩平、笠井清登、福田正人	気分障害のNIRS研究と臨床への応用	臨床精神医学	In press		2009
滝沢龍、笠井清登、川久保友紀、丸茂浩平、川崎真護、山末英典、福田正人	統合失調症における前頭極と機能障害との関連 －多チャンネル近赤外線スペクトロスコピー（NIRS）研究－.	脳と精神の医学	In press		2009
笠井清登、滝沢龍	統合失調症の神経画像研究	精神医学	51（2）	177－184	2009
Masako Okamoto, Haruka Dan, Lester Clowney, Yui Yamaguchi, Ippeita Dan	Activation in ventro-lateral prefrontal cortex during the act of tasting: an fNIRS study	Neuroscience Letters	451	129-133	2009
Masako Okamoto, Daisuke Tsuzuki, Lester Clowney, Haruka Dan, Archana K. Singh, Ippeita Dan	Structural atlas-based spatial registration for functional near-infrared spectroscopy enabling inter-study data integration	Clinical Neurophysiology		In press	2009
Hashimoto R, Mori T, Nemoto K, Moriguchi Y, Noguchi H, Nakabayashi T, Hori H, Harada S, Kunugi H, Saitoh O, Ohnishi T.	Abnormal microstructures of the basal ganglia in schizophrenia revealed by diffusion tensor imaging.	World J Biol Psychiatry.	10	65-69	2009
Hashimoto R, Moriguchi Y, Yamashita F, Mori T, Nemoto K, Okada T, Hori H, Noguchi H, Kunugi H, Ohnishi T	Dose-dependent effect of the Val66Met polymorphism of the brain-derived neurotrophic factor gene on memory-related hippocampal activity	Neurosci Res	61	360-367	2008
Moriguchi Y, Ohnishi T, Decety J, Hirakata M, Maeda M, Matsuda H, Komaki G	The human mirror neuron system in a population with deficient self-awareness: An fMRI study in alexithymia	Hum. Brain Mapp.	in press		
根本清貴	単一光子放射断層撮影（SPECT）による脳機能評価	Medical Technology	37	236-240	2009
Matsuo, K., Nicoletti, M., Nemoto, K., Hatch, J.P., Peluso, M.A., Nery, F.G., Soares, J.C.	A voxel-based morphometry study of frontal gray matter correlates of impulsivity	Hum. Brain Mapp.	in press		

Yasmin, H., Nakata, Y., Aoki, S., Abe, O., Sato, N., Nemoto, K., Arima, K., Furuta, N., Uno, M., Hirai, S., Masutani, Y., Ohtomo, K.	Diffusion abnormalities of the uncinate fasciculus in Alzheimer's disease: diffusion tensor tract-specific analysis using a new method to measure the core of the tract	Neuroradiology	50	293-299	2008
根本清貴	最新のMRI脳画像 Voxel Based Morphometry	認知神経科学	10	28-32	2008
Kasai K, Yamasue H et al	Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder.	Biological Psychiatry	63	550-556	2008
Yamasue H et al.	Gender-common and -specific neuroanatomical basis of human anxiety-related personality traits.	Cerebral Cortex	18	46-52	2008
Asami T et al.	Anterior cingulate cortex volume reduction in patients with panic disorder.	Psychiatry Clin Neurosci	62	322-330	2008
Takizawa R et al.	Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study.	Schizophrenia Research	99	250-262	2008
Abe O et al.	Comparison of gray/white matter volume and diffusion tensor data.	Neurobiology of Aging	29	102-116	2008
Yamasue H et al.	Sex-Linked neuroanatomical basis of human altruistic cooperativeness.	Cerebral Cortex	18	2331-2340	2008
Yamasue H et al.	Association between mitochondrial DNA 10398A>G polymorphism and the volume of amygdale.	Genes, Brain and Behaviour	7	698-704	2008
Takei K, Yamasue H et al.	Disrupted integrity of the fornix is associated with impaired memory organization in schizophrenia.	Schizophrenia Research	103	52-61	2008
Asami T, Yamasue H et al.	Sexually dimorphic gray matter volume reduction in patients with panic.	Psychiatry Research Neuroimaging			Inpress
Yamasue H et al.	Oxytocin, Sexually-dimorphic feature of social brain, and Autism.	Psychiatry Clin Neurosci			Inpress
Kunimatsu N et al.	Tract-specific analysis of the superior occipitofrontal fasciculus in schizophrenia.	Psychiatry Res	164(3)	198-205	2008
Sasaki H et al.	Structural and diffusional brain abnormality related to relatively low level of alcohol consumption.	NeuroImage			Inpress
浅見剛 ほか	統合失調症におけるロールシャッハ・テストと脳形態変化　認知的媒介スコアと形態変化、Optimized VBMによる検討.	脳と精神の医学	19	41-49	2008
阿部修 ほか	単極性うつ病における灰白質・白質容積と拡散テンソルに関するボクセルベース解析.	日本磁気共鳴医学会雑誌	28	35-40	2008

豊田英真, 山末英典 ほか	軽度の意識障害を伴う精神病状態を呈した多発性内分泌腫瘍1型の症例.	精神神経学雑誌	110	517	2008
杉下和行, 山末英典 ほか	単純型統合失調症と診断されていたが、併存する睡眠時無呼吸症候群に対する持続陽圧呼吸療法により、倦怠感などの精神症状が軽快した1例.	精神神経学雑誌	110	514-515	2008
岡田悠子, 山末英典 ほか	薬剤性パーキンソニズムが出現しやすくパーキンソン病との鑑別が困難だったうつ病の1例.	精神神経学雑誌	110	513	2008
岡田直大, 山末英典 ほか	羽ばたき振戦を伴う精神病症状の増悪を呈し,抗てんかん薬と抗精神病薬の減量で症状軽快した統合失調症の1例.	精神医学	50	905-908	2008
阿部修, 山末英典 ほか	最新のMRI脳画像 拡散テンソル画像のSPM解析.	認知神経科学	10	33-38	2008
山末英典 ほか	統合失調症の病態生理:脳機能・脳画像による解析 統合失調症の病態解明から病因解明へ.	認知神経科学	10	23-27	2008
山末英典	発達障害の病態と治療　広汎性発達障害と注意欠陥多動性障害を中心に 広汎性発達障害における社会性の障害の脳基盤.	精神神経学雑誌	2008 特別	S-131	2008
Hashimoto K, Ishima T, Fujita Y, Matsuo M, Kobashi T, Takahagi M, Tsukada H, Iyo M.	Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the novel selective α7 nicotinic receptor agonist SS	Biol. Psychiatry	63	92-97	2008
Karasawa J, Hashimoto K, Chaki S	D-serine and a glycine transporter inhibitor improve MK-801-induced cognitive deficits in a novel object recognition test in rats.	Behav. Brain Res.	186	78-83	2008
Suzuki K, Nakamura K, Iwata Y, Sekine Y, Kawai M, Sugihara G, Tsuchiya KJ, Suda S, Matsuzaki H, Takei N, Hashimoto K, Mori, N.	Decreased expression for the reelin receptor VLDLR in peripheral lymphocytes of drug naive schizophrenic patients.	Schizophrenia Res	98	148-156	2008
Fujita Y, Ishima T, Kunitachi S, Hagiwara H, Zhang L, Iyo M, Hashimoto K.	Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antibiotic drug minocycline.	Prog. Neuropsychopharmacol. Biol. Psychiatry	32	336-339	2008
Takeshita M, Yamada K, Hattori E, Iwayama Y, Toyota T, Iwata Y, Tsuchiya KJ, Sugihara G, Hashimoto K, Watanabe H, Iyo M, Ikuchi M, Okazaki Y, Yoshikawa T.	Genetic examination of the PLXNA2 gene in Japanese and Chinese schizophrenics.	Schizophrenia Res.	99	359-364	2008
Sakata M, Kimura Y, Naganawa M, Ishikawa M, Oda K, Ishii K, Hashimoto K, Chihara K, Ishiwata K.	Shortened protocol in practical [^{11}C]SA4503-PET studies for the sigma-1 receptor quantification.	Ann. Nucl. Med.	22	143-146	2008

Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, Takanashi J, Matsuda T, Shimizu E, Ikehira H, Iyo M, Hashimoto K.	Negative correlation between brain glutathione levels and negative symptoms in schizophrenia: a 3T ^{1}H-MRS study.	PLoS ONE	3	e1944	2008
Hikida T, Mustafa AK, Maeda K, Fujii K, Barrow RK, Saleh M, Oby L, Huganir RL, Snyder SH, Hashimoto K, Sawa A.	Modulation of D-serine levels in brains of mice lacking PICK1	Biol. Psychiatry	63	997-1000	2008
Hashimoto K, Fujita Y, Ishima T, Chaki S, Iyo M.	Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of glycine transporter-1 inhibitor NFPS and D-serine.	Eur. Neuropsychopharmacol.	18	414-421	2008
Hagiwara H, Fujita Y, Ishima T, Kunitachi S, Shirayama Y, Iyo M, Hashimoto K.	Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antipsychotic drug perospirone: role of serotonin 5-HT$_{1A}$ receptor.	Eur. Neuropsychopharmacol.	18	448-454	2008
Iyo M, Shirayama Y, Watanabe H, Fujisaki M, Miyatake R, Fukami G, Shiina A, Nakazato M, Shiraishi T, Ookami T, Hashimoto K.	Fluvoxamine as a sigma-1 receptor agonist improved cognitive impairments in a patient with schizophrenia.	Prog. Neuropsychopharmacol. Biol. Psychiatry	32	1072-1073.	2008
Iwata Y, Suzuki K, Wakuda T, Seki N, Thanseem I, Matsuzaki H, Mamiya T, Ueki T, Mikawa S, Sasaki T, Suda S, Yamamoto S, Tsuchiya KJ, Sugihara G, Nakamura K, Sato K, Takei N, Hashimoto K, Mori N.	Irradiation at adulthood as a new model of schizophrenia.	PLoS ONE	3	e2283	2008
Kanahara N, Shimizu E, Ohgake S, Fujita Y, Kohno M, Hashimoto T, Matsuzawa D, Shirayama Y, Hashimoto K, Iyo M.	Glycine and D-serine, but not D-cycloserine, attenuate prepulse inhibition deficits induced by NMDA receptor antagonist MK-801.	Psychopharmacology	198	363-374.	2008
Fujita Y, Ishima T, Horio M, Hagiwara H, Iyo M, Hashimoto K.	Alterations in plasma levels of amino acids after intracerebroventricular administration of L-serine or D-serine in conscious and freely moving rats.	Open. Clin. Chem. J.	1	22-26	
Ferraris, D., Duvall, B., Ko, Y.S., Thomas, A.G., Rojas, C., Majer, P., Hashimoto, K. and Tsukamoto, T.	Synthesis and biological evaluation of D-amino acid oxidase inhibitors.	J. Med. Chem.	51	3357-3359.	2008
Nishimura, T., Ishima, T., Iyo, M. and Hashimoto, K.	Potentiation of nerve growth factor-induced neurite outgrowth by fluvoxamine: role of sigma-1 receptors, IP3 receptors and cellular signaling pathways.	PLoS ONE	3	e2558	2008
Hashimoto, K.	Editorial: CSF serine enantiomers and glycine in the study of neurologic and psychiatric disorders.	Clin. Chemistry	54	1413-1414.	2008

Ishima, T., Nishimura, T., Iyo, M. and Hashimoto, K.	Potentiation of nerve growth factor-induced neurite outgrowth in PC12 cells by donepezil: role of sigma-1 receptors and IP3 receptors.	Prog. Neuropsychopharmacol. Biol. Psychiatry	32	1656-1659	2008
Hashimoto, K.	Microglial activation in schizophrenia and minocycline treatment.	Prog. Neuropsychopharmacol. Biol. Psychiatry	32	1758-1759.	2008
Hashimoto, K., Nishiyama, S., Ohba, H., Matsuo, M., Kobashi, T., Takahagi, M., Iyo, M., Kitashoji, T. and Tsukada, H.	[^{11}C]CHIBA-1001 as a novel PET ligand for α7 nicotinic receptors in the brain: A PET study in conscious monkeys.	PLOS ONE	3	E3231	2008
Hahsimoto, K.	Correspondence: Regarding "N-Acetyl cysteine as a glutathione precursor for schizophrenia – a double-blind, randomized, placebo-controlled trial".	Biol. Psychaitry	64	E1	2008
Inoue, R., Hashimoto, K., Harai, T. and Mori, H.	NMDA- and β-amyloid$_{1-42}$-induced neurotoxicity is attenuated in serine racemase knockout mice.	J. Neurosci.	28	14486-14491	2008
Hahsimoto, K.	Reply to: Minocycline, schizophrenia and GluR1 glutamate receptors.	Prog. Neuropsychopharmacol. Biol. Psychiatry	33	167	2008
Ishima, T., Fujita, Y., Kohno, M., Kunitachi, S., Horio, M., Takatsu, M., Minase, T., Tanibuchi, Y., Hagiwara, H., Iyo, M. and Hashimoto, K.	Improvement of phencyclidine-induced cognitive deficits in mice by subsequent subchronic administration of fluvoxamine, but not sertraline.	The Open. Clin. Chem. J.	2	7-11	2009
Matsuzawa, D., Hashimoto, K., Hashimoto, T., Shimizu, E., Watanabe, H., Fujita, Y. and Iyo, M.	Association study between the genetic polymorphisms of glutathione-related enzymes and schizophrenia in a Japanese p	Am. J. Med. Genet. Part B	150B	86-97	2009
Kanahara, N., Iyo, M. and Hashimoto, K.	Failure to confirm the association between the PIK4CA gene and schizophrenia in a Japanese population.	Am. J. Med. Genet. Part B	150B	In press	2009
Hashimoto K.	Nausea associated with a nicotinic agonist therapy in schizophrenia.	Clin. Psychopharmacol. Neurosci.		In press	2009
Hashimoto, K., Fujita, Y., Horio, M., Kunitachi, S., Iyo, M., Ferraris, D. and Tsukamoto, T.	Co-administration of D-amino acid oxidase inhibitor potentiates the efficacy of D-serine on prepulse inhibition deficits after administration of dizocilpine.	Biol. Psychiatry		In press	2009
Hashimoto K.	Sigma-1 receptors and selective serotonin reuptake inhibitors: clinical implications of their relationship.	CNS Agents – Med. Chem.		In press	2009

Kanahara, N., Shimizu, E., Sekine, Y., Uchida, Y., Shibuya, T., Yamanaka, H., Hashimoto, T., Asaka, T., Sasaki, T., Miyatake, R., Ohkamia, T., Fukami, G., Fujisaki, M., Watanabe, H., Shirayama, Y., Hayashi, H., Hashimoto, K., Asano, M. and Iyo M	Does hypofrontality expand to global brain area in progression of schizophrenia? : A cross-sectional study between first-episode and chronic schizophrenia.	Prog. Neuropsychopharmacol. Biol. Psychiatry		In press	2009
Toyohara, J., Sakata, M., Wu, J., Ishikawa, M., Oda, K., Ishii, K., Iyo, M., Hashimoto, K. and Ishiwata, K.	Preclinical and the first clinical studies on [^{11}C]CHIBA-1001 for mapping α7 nicotinic receptors by positron emission tomography.	Ann. Nul. Med.		In press	2009
Takizawa, R., Hashimoto, K., Tochigi, M., Kawakubo, Y., Marumo, K., Sasaki, T., Fukuda, M. and Kasai, K.	Association between sigma-1 receptor gene polymorphism and prefrontal hemodynamic response induced by cognitive activation in schizophrenia.	Prog. Neuropsychopharmacol. Biol. Psychiatry		In press	2009
Ohgake, S., Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Koizumi, H., Fujisaki, M., Kanahara, N., Matsuzawa, D., Muramatsu, H., Muramatsu, T. and Iyo, M.	Dopaminergic hypofunctions and prepulse inhibition deficits in mice lacking midkine.	Prog. Neuropsychopharmacol. Biol. Psychiatry		In press	2009
Hashimoto, K.	Comments to "An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder".	J. Clin. Psychopharmacol.		In press	2009

Ⅳ．　研究成果の別刷

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Regular Article

Risk of developing schizophrenia among Japanese high-risk offspring of affected parent: outcome of a twenty-four-year follow up

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Aims: Prospective follow-up studies of high-risk children may help clarify the etiological factors in schizophrenia. While studies from North America, Europe and Israel have estimated the risk of schizophrenia at 7–16% in the offspring of an affected parent, no data have been reported for Asian populations.

Method: We started a follow up of the offspring of Japanese schizophrenia patients in 1978. We investigated the estimated risk of schizophrenia in 51 high-risk offspring at the 24-year follow up. The effects of the parents' status, including history of psychiatric hospitalization and social functioning, on the risk in the offspring were also investigated.

Results: The cumulative incidence of schizophrenia was 13.7 % and the lifetime prevalence was estimated to be 13.5 ± 4.8%. The association between the psychiatric hospitalization in the probands and the risk of schizophrenia in the offspring was not significant, and the Global Assessment of Functioning score was significantly lower in the probands with a history of psychiatric hospitalization than in those without such a history.

Conclusions: The risk of developing schizophrenia in Japanese high-risk offspring might be comparable with the Western results. The present study suggests that the severity of the disease or the level of social functioning may not significantly affect the risk in Japanese offspring.

Key words: genetic factors, high-risk offspring, Japanese, prospective follow up, schizophrenia.

WHILE THE LIFETIME risk of developing schizophrenia is approximately 1% in the general population, family studies have shown that the risk may be more than ten times higher in the offspring of a parent suffering from schizophrenia (high-risk offspring).[1] These family studies of schizophrenia were mainly from Europe and North America, and few studies involved an Asian population.[2,3] The elevated risk of schizophrenia in high-risk offspring is considered to be basically a genetic mechanism.[4] However, the specific factors at work remain to be clarified. Environmental factors, which could interact with the genetic factors, might also play a role in the elevation of the risk. Such environmental factors might include the child's upbringing environment and the parents' mental status[5] as well as several biological factors present in the environment during the early developmental stages.[6]

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High-risk studies of schizophrenia prospectively follow the offspring born to parents with the disease (high-risk offspring) from early developmental stages to adulthood. This strategy helps estimate the risk of psychosis in the high-risk offspring. It also helps search for the etiological factors of schizophrenia and for clues to its prevention.[7] Thus far, several groups from Europe, North America and Israel have conducted high-risk studies of schizophrenia (reviewed by Cannon *et al.*).[8] The cumulative incidence of schizophrenia was estimated as follows in those studies: 8.3% in the USA,[9] 16.2% in Denmark,[10] 8.0% in Israel,[11] 13.1% in the USA,[12] 3.6% in Sweden[13] and 6.7% in Finland.[14] With the exception of an incidence of 3.6% in Sweden,[12] the incidence ranged from 6.7% (in Finland)[14] to 16.2% (in Denmark).[10] While this relatively wide range may be due to chance or to differences in the estimating methods,[7] it could be partly due to differences in the clinical features of the affected parents or in the epidemiological backgrounds among the studies.[8]

Here we report the 24-year outcome of our high-risk study of schizophrenia in Japan ('The Tokyo Schizophrenia High-Risk Study'). The follow up was started in 1978, and the last survey of the subjects was completed at the end of 2003. A major aim of the present study is to examine whether the risk of developing schizophrenia in Japanese high-risk offspring is comparable with the risk in European, North American or Israeli high-risk offspring. This is the first high-risk study of schizophrenia in Asia. No other Japanese or Asian study has thus far investigated the long-term outcome for high-risk offspring with a prospective follow up.

Another aim of the present study is to examine whether attributes of the affected parents, including social functioning and the presence/absence of psychiatric hospitalization, modify the risk of schizophrenia in high-risk offspring. A previous study observed that the risk of schizophrenia might differ between offspring who grew up in nursing institutions and those who were reared at home.[15] The upbringing environment may have an effect on the future precipitation of the disease.[5,11,15] The severity of the parents' illness may also biologically or psychologically affect the risk in the offspring.[16] In the present subjects, half of the affected parents (the probands) had no history of psychiatric hospitalization at the start of the follow up. The probands were recruited at the authors' outpatient clinic and were under the care of the authors for most of the follow-up period. This may be a unique feature of the present study in contrast with the previous studies, which mainly followed up hospitalized patients and their offspring.[9–14] Thus, in the present study, the high-risk offspring were all being reared at home by their biological parents at the start of the follow up. Whether these features of our study significantly affect the risk of schizophrenia in the offspring is of interest.

METHOD

Recruitment of the probands

The probands were recruited at the outpatient clinic of the principal investigator (Y. O.), at the Department of Psychiatry, University of Tokyo Hospital, during the period 1978–1985. Those who met the following criteria were invited to participate in the study: (i) diagnosed with schizophrenia according to the Ninth Revision of the International Classification of Disease criteria;[17] (ii) ethnically Japanese (i.e. with parents in whom no ethnicity other than Japanese was present); (iii) without a comorbidity of alcoholism, any other substance-related disorder, or organic mental disorders; (iv) having one or more healthy child aged ≦18 years at the time of recruitment; and (v) being married with a spouse who was the biological parent of the child and was living with the spouse and the children in the Tokyo area. Among 36 patients who met the criteria, agreement was obtained from 35 patients (six male and 29 female) and their spouses to participate in the study.

The procedure of the diagnostic assessment can be briefly described as follows. At the recruitment, the proband was interviewed and clinical records were reviewed separately by two of the authors including Y. O., and a consensus diagnosis was made. The diagnosis was reconfirmed 5–10 years after the start of the follow up considering the clinical course, and a final consensus diagnosis was made according to the Diagnostic and Statistical Manual of mental Disorders (Third Edition, Revised) (DSM-III-R) criteria[18] in 1992 by three authors (T. S., S. H. and Y. O.). Among the initial 35 probands, four were finally diagnosed with schizoaffective disorder and one with delusional disorder. These five subjects were excluded from the follow up at this point, and we continued to follow up the 30 probands diagnosed with DSM-III-R schizophrenia (four male and 26 female, age (mean ± SD) = 47.8 ± 5.2 years as of 1992). At the

time of recruitment, 15 (two male and 13 female) of the 30 probands had no history of psychiatric hospitalization. Spouses of the probands were also interviewed, and their mental status was evaluated by Y. O. from1986–1992. All the spouses were confirmed not to be suffering from schizophrenia or other major psychoses.

Recruitment of the high-risk offspring

Follow up of 65 offspring of the initial 35 probands was started between 1978 and 1985. Out of the total of 65, ten offspring born to the five probands whose final diagnosis was not schizophrenia were excluded. Therefore, the follow up of 55 offspring (27 male and 28 female) was continued after the final diagnosis of the probands in 1992. The ages of the 55 offspring at the start of the follow up were as follows: 16 newborns, 15 aged 1–5 years, 16 aged 6–10 years, six aged 11–15 years and two aged 16–18 years (mean ± SD = 5.5 ± 5.6 years).

Follow up of the high-risk offspring and probands

All the probands were regularly cared for by one of the authors at psychiatric outpatient clinics in Tokyo until the mid-1990s. When the care at the authors' clinics was discontinued, yearly contact by telephone or mail was begun. Also, the probands and their families were welcome to contact the authors when they wanted advice on or help with their treatment or with other concerns including the care of their offspring, especially when risky situations arose (e.g. school refusal and withdrawal). In addition to these frequent contacts, detailed investigations of the subjects' outcomes were twice conducted during the follow up. The first investigation was performed during the period 1992–1994. The second investigation was conducted approximately ten years after the first investigation (2002–2003, (mean ± S.D.) follow-up period = 23.7 ± 3.5 years). In these investigations, one or two authors visited the homes of the subjects and interviewed the probands, offspring and, in some cases, the spouses. When the subjects were not amenable to a visit, a telephone interview of the proband and the family was conducted. In the first investigation, the authors were able to visit all of the probands and families. In the second investigation, however, five probands with ten offspring were telephone-interviewed. When the offspring or probands were under the care of other mental health professionals, the authors asked the caregivers to collect the information, with the subjects' agreement. According to the information gathered through the regular contacts and the investigations, three authors including Y. O. evaluated whether the high-risk offspring developed psychotic disorders, including schizophrenia, schizoaffective disorder, mania and major depression with psychotic features, according to the DSM-III-R criteria. The mental condition and social functioning of the probands were assessed using the Global Assessment of Functioning (GAF) Scales[19] in the second investigation.

Informed consent and ethical review

The objective of the study was explained, and informed consent was obtained from the probands and spouses at the initial recruitment and in the outcome surveys during the follow up. Consent was also obtained from the offspring when they were ten years old or older. The study was approved by the ethical boards of the faculties of medicine at the University of Tokyo and Mie University.

Statistical analysis

Association between the proband's features and the development of psychosis in the offspring was analyzed using the χ^2 or Fisher's exact test. The cumulative incidence of psychosis in the offspring was calculated as of the end of 2003. Lifetime morbidity risk and survival probability were estimated with age correction using the Kaplan–Meier method. These analyses were conducted using SPSS, 11.0.

RESULTS

Outcome of the probands

The 24-year follow up was completed in 29 probands (four male and 25 female) out of the 30. A female proband with one female offspring dropped out after 10 years of follow up when they moved to a distant area. When the follow up was stopped in this case, the offspring was 21 years old and had not developed any of the psychotic disorders.

Out of the 29 probands, two (one male and one female) died due to suicide. Six others (one male and five female) experienced psychiatric hospitalization due to the exacerbation of schizophrenia during the

Table 1. The demographic characteristics of the proband with or without affected offspring

	Proband with affected offspring ($n = 7$)	Proband without affected offspring ($n = 21$)	Test statistics	*P*-value
Gender, *n* (%)				
Male	2	2		ns†
Female	5	19		
Probands with psychiatric hospitalization, *n* (%)	4 (57.1)	11 (52.4)		ns†
GAF score: mean (SD)	54.5 (13.8)	55.9 (19.1)	0.16‡	ns

†Fisher's exact test. ‡Independent *t*-test. GAF, Global Assessment of Functioning; ns, not significant.

follow up. Two (both female) of these six had no history of hospitalization before the start of the follow-up. Thus, 13 probands (two male and 11 female) out of the 29 had no experience of psychiatric hospitalization when the follow-up was completed. Four probands (all female) were divorced or separated from their spouses, and three of the four experienced no hospitalization during the follow up.

Risk of the psychoses in the offspring

Out of the 55 offspring, the follow up was stopped in four offspring (two male and two female) before any psychotic disorders had developed. Among the four, two male offspring died of physical illnesses (leukemia and heart failure) at the ages of 17 and 30, respectively. Two female offspring dropped out of the follow up at the ages of 21 and 22, when one moved to a distant area with her family and the proband of the other died.

Thus, the follow up was completed in 51 high-risk offspring (25 male and 26 female), who were born to 28 probands (four male and 24 female). The age of the offspring ranged from 18 to 43 years (mean ± SD = 29.2 ± 6.4) at the end of the follow up. Out of the 51 offspring, seven (three male and four female, two from affected fathers and five from affected mothers, [Table 1]) developed a psychotic disorder by the end of 2003. All of them were diagnosed with schizophrenia according to the DSM-III-R criteria. The cumulative incidence of schizophrenia was therefore 13.7% (95% CI = 6.8 – 25.7%). The age at onset was 15 years in two, 18 years in one, 19 years in three and 22 years in one offspring. The age-corrected lifetime morbidity risk using the Kaplan–Meier method was estimated to be 13.5 ± 4.8 %. The accumulated hazard curve using the Kaplan–Meier method is shown in Figure 1. An analysis according to the sex of the proband showed that among the offspring of the affected mothers ($n = 39$, cumulative incidence = 12.8 %: [95% CI = 5.6 – 26.7 %]), five developed schizophrenia, while out of the 12 offspring of the affected fathers two (17%) developed the disease.

The risk of schizophrenia in the offspring according to the proband's history of psychiatric hospital-

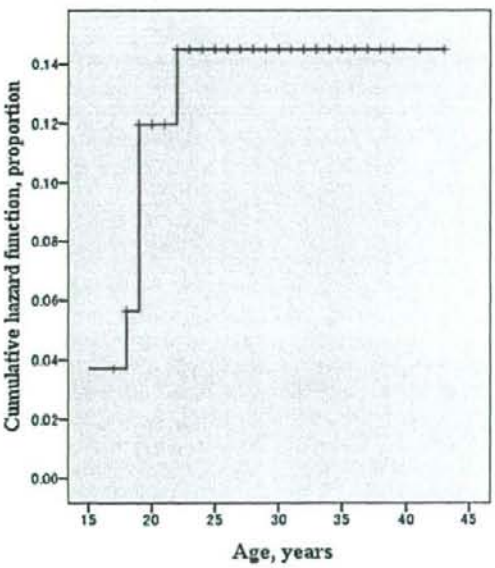

Figure 1. Age-corrected risk of developing schizophrenia in high-risk offspring.

Table 2. Comparison of the GAF scores and the rates of the affected offspring between proband with and without history of psychiatric hospitalization at the end of the 24-year follow-up

History of psychiatric hospitalization	Number of probands	GAF score mean (SD)	*P*-value[†]	Rate of affected offspring Affected / total (%)	*P*-value[‡]
(+)	15	48.6 (19.0)	0.031	4/27 (14.8%)	ns
(−)	13	63.1 (13.3)		3/24 (12.5%)	

[†]Independent *t*-test. [‡]Fisher's exact test. GAF, Global Assessment of Functioning; ns, not significant.

ization is summarized in Table 2. Among the 51 offspring, 27 were from probands with a history of hospitalization ($n = 15$) and 24 were from probands without such a history ($n = 13$). Out of the 27 offspring of probands with a hospitalization history, four developed schizophrenia (14.8%), while out of the 24 offspring of probands without such a history, three (12.5%) developed the disease. No significant difference was observed in the risk of schizophrenia between the offspring of probands with a hospitalization history and the offspring of those without (14.8% vs 12.5%, $P = 1$, Fisher's exact test). Age was not significantly different between the 27 offspring of probands with a history and the 24 offspring of those without (29.3 ± 5.9 years vs 29.1 ± 7.0 years [mean ± SD] at the end of the follow up). GAF scores were significantly different between the probands with and without a hospitalization history (48.6 ± 19.0 and 63.1 ± 13.3 [mean ± SD], respectively) at the second investigation ($t = 2.2$, d.f. = 25, $P = 0.03$). When the probands with and without affected offspring ($n = 6$ and 21, respectively) were compared, the GAF scores were not significantly different (54.5 ± 13.8 vs 55.9 ± 19.1 (mean ± SD), respectively, $t = 0.16$, d.f. = 25, $P = 0.87$) (Table 1).

DISCUSSION

The present study investigated the risk of schizophrenia in the offspring of affected parents in the Japanese population. This is the first Asian high-risk study of schizophrenia, to our knowledge. The risk of developing schizophrenia was approximately 14% in the Japanese high-risk offspring. The cumulative incidence was 13.7% (95% CI = 6.8 – 25.7%), with an estimated lifetime risk of 13.5 ± 4.8%. In Western studies, the incidence has been reported to range from 6.7% to 16.2%.[14] The risk of developing schizophrenia in Japanese high-risk offspring might therefore be comparable with the average of the reported rates or rather close to the two highest rates (13.1% in the study by Erlemeyer-Kimling *et al.*, 1997,[12] 16.3% in that by Parnas *et al.*, 1993[10] among the Western studies).

Approximately half of the probands (13 out of 28) never experienced psychiatric hospitalization. The disease, therefore, might not, on average, be severe in the present probands. This lack of severity did not appear to lower the risk in Japanese offspring, considering the relatively high incidence or lifetime-risk. In addition, the association between the presence/absence of psychiatric hospitalization in the probands and the risk of schizophrenia in the offspring (12.5% vs 14.8%, respectively) was not significant, while the GAF score was significantly lower in the probands with a history of psychiatric hospitalization than in those without such a history. These findings suggest that the severity of the disease or the level of social functioning may not significantly affect the risk in Japanese offspring. The present offspring were all raised at home by their biological parents. Therefore, a poor upbringing environment due to hospitalization of the parents or to the parent's lower social functioning might not significantly change the risk of schizophrenia in the offspring in the present sample.

We maintained close contact with the probands and their families. The probands were recruited at the authors' clinic and were clinically cared for for several years, as in the study by Fish.[9] Regular contacts were continued if the probands moved to other clinics. The probands and spouses were welcome to ask the authors for help and advice on clinical and other mental health issues. This enabled us to continue close observation of the probands and families for more than 20 years. We were thus able to determine the onset of psychosis in the offspring using direct information from the families. This unique feature of the study might have helped us to achieve a high follow-up rate (93.0% or 51 out of 55 offspring). We

are not able to evaluate the effects of this close care on the outcome of the proband and the rate of the development of psychoses in the offspring, because control data without the close care is not available in our sample.

A limitation of the present study may be the relatively small sample size, which resulted in the large 95% confidence interval of the cumulative incidence (6.8 – 25.7%) by reducing the statistical power. No significant association was observed in the present study between the risk in the offspring and the psychiatric hospitalization or social functioning of the proband. This finding could also be related to the lack of statistical power.

Another limitation is that we did not employ a structured interview. Information was mainly obtained for the psychiatric assessment from clinical interviews/records and from regular contacts with the probands and families. This is why we focused on the risk of psychotic disorders including schizophrenia and did not study other mental disorders in the offspring. Finally, the age of the offspring ranged from 18 to 43 years as of the end of the follow up. This range may be larger than those in previous studies. Considering these limitations, the present results should be interpreted with caution.

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REFERENCES

[1] Gottesman II, Shields J. *The Epigenetic Puzzle*. Cambridge University Press, New York, 1982.
[2] Imamura A, Honda S, Nakane Y, Okazaki Y. Anticipation in Japanese families with schizophrenia. *J. Hum. Genet.* 1998; **43**: 217–223.
[3] Somnath CP, Janardhan Reddy YC, Jain S. Is there a familial overlap between schizophrenia and bipolar disorder? *J. Affect. Disord.* 2002; **72**: 243–247.
[4] Gottesman II. *Schizophrenia Genesis: The Origin of Madness*. W.H. Freeman and Co. New York, 1991.
[5] Wahlberg KE, Wynne LC, Hakko H *et al.* Interaction of genetic risk and adoptive parent communication deviance: Longitudinal prediction of adoptee psychiatric disorders. *Psychol. Med.* 2004; **34**: 1531–1541.
[6] Tochigi M, Okazaki Y, Kato N, Sasaki T. What causes seasonality of birth in schizophrenia? *Neurosci. Res.* 2004; **48**: 1–11.
[7] Niemi LT, Suvisaari JM, Tuulio-Henriksson AM, Lonnqvist JK. Review. Childhood developmental abnormalities in schizophrenia: Evidence from high-risk studies. *Schizophr. Res.* 2003; **60**: 239–258.
[8] Cannon M, Tarrant CJ, Huttunen MO, Jones P. Childhood development and later schizophrenia: Evidence from genetic high-risk and birth cohort studies. **In**: Murray R, Jones PB, Susser E, van Os J, Cannon M (eds). *The Epidemiology of Schizophrenia*. Cambridge University Press, Cambridge, 2003; 100–123.
[9] Fish B. Infant predictors of the longitudinal course of schizophrenic development. *Schizophr. Bull.* 1987; **13**: 395–409.
[10] Parnas J, Cannon TD, Jacobsen B, Schulsinger F, Mednick SA. Lifetime DSM-III R diagnostic outcomes in the offspring of Schizophrenic mothers: Result from the Copenhagen High-Risk Study. *Arch. Gen. Psychiatry* 1993; **50**: 707–714.
[11] Ingraham LJ, Kugelmass S, Frenkel E, Nathan M, Mirsky AF. Twenty-five-year follow-up of the Israeli High-risk Study: Current and lifetime psychopathology. *Schizophr. Bull.* 1995; **21**: 183–192.
[12] Erlenmeyer-Kimling L, Adamo UH, Rock D *et al.* The New York High-Risk Project: Prevalence and comorbidity of axis I disorders in offspring of schizophrenic patients at 25-year follow-up. *Arch. Gen. Psychiatry* 1997; **55**: 1096–1102.
[13] Schubert ED, McNeil TF. Prospective study of adult mental disturbance in offspring of women with psychosis. *Arch. Gen. Psychiatry* 2003; **60**: 473–480.
[14] Niemi LT, Suvisaari JM, Haukka JK, Wrede G, Lonnqvist JK. Cumulative incidence of mental disorders among offspring of mothers with psychotic disorder: Result from the Helsinki High-Risk Study. *Br. J. Psychiatry* 2004; **185**: 11–17.
[15] Parnas J, Teasdale TW, Schulsinger H. Institutional rearing and diagnostic outcome in children of schizophrenic mothers. A prospective high-risk study. *Arch. Gen. Psychiatry* 1985; **42**: 762–769.
[16] Jorgensen A, Teasdale TW, Parnas J, Schulsinger F, Schulsinger H, Mednick SA. The Copenhagen high-risk project. The diagnosis of maternal schizophrenia and its relation to offspring diagnosis. *Br. J. Psychiatry* 1987; **151**: 753–757.
[17] World Health Organization. *Mental Disorder Glossary and Guide to their Classification in Accordance with the Ninth Revision of the International Classification of Disease (ICD-9)*. WHO, Geneva, 1978.
[18] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. American Psychiatric Association, Washington, DC, 1987.
[19] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. American Psychiatric Association, Washington, DC, 1994.