ORIGINAL ARTICLE

Cognitive and Magnetic Resonance Imaging Brain Morphometric Correlates of Brain-Derived Neurotrophic Factor Val66Met Gene Polymorphism in Patients With Schizophrenia and Healthy Volunteers

Beng-Choon Ho, MRCPsych; Peter Milev, MD, PhD; Daniel S. O'Leary, PhD; Amy Librant, BS; Nancy C. Andreasen, MD, PhD; Thomas H. Wassink, MD

Context: Relatively little is known about genetic determinants of cognitive dysfunction in schizophrenia. Recent studies suggest that a brain-derived neurotrophic factor (BDNF) prodomain single nucleotide polymorphism resulting in a valine (Val)–to–methionine (Met) substitution is associated with impaired declarative memory in healthy volunteers and patients with schizophrenia. These studies indicate that the $BDNF_{Met}$ variant may mediate hippocampal cognitive functions by modulating intracellular trafficking and activity-dependent BDNF release. To our knowledge, the way in which this functional single nucleotide polymorphism affects other neurocognitive measures has not been examined. Its role in determining cognitive deficits in schizophrenia has also not been systematically studied.

Objectives: To characterize the neurocognitive and brain morphometric phenotypic correlates of the BDNF Val66Met polymorphism and to test the specificity of the $BDNF_{Met}$ variant on cognitive dysfunction in schizophrenia.

Design, Setting, and Participants: A comprehensive battery of standardized neuropsychological tests was administered to 144 healthy volunteers and 293 patients with schizophrenia spectrum disorder at a tertiary care university hospital. Approximately two thirds of the sample also underwent high-resolution magnetic resonance imaging brain scans.

Main Outcome Measures: Genotype effects (in Met allele carriers vs Val homozygotes) on 5 cognitive domain *z* scores and magnetic resonance imaging gray matter brain volume measures (Talairach atlas–based cerebral lobes and optimized voxel-based morphometry) were examined using general linear models.

Results: On verbal memory, there was a significant genotype effect but no genotype × diagnosis effects. In both patients with schizophrenia and healthy volunteers, Met allele carriers had poorer verbal memory performance than their Val-homozygous counterparts. On visuospatial abilities, there were significant genotype and genotype × diagnosis effects. Met allele–associated visuospatial impairment was specific to patients with schizophrenia but not healthy volunteers. There were significant genotype effects on gray matter volumes within brain regions known to subserve these 2 cognitive domains, with Met allele carriers having smaller temporal and occipital lobar gray matter volumes. Optimized voxel-based morphometry further suggests that parietal heteromodal cortical gray matter deficits may underlie visuospatial impairment in patients with schizophrenia carrying the Met allele.

Conclusions: We replicated the association between the $BDNF_{Met}$ variant and poor medial temporal lobe–related memory performance. The consonance of our cognitive and brain morphology findings further suggests that the $BDNF_{Met}$ variant may have a specific role in conferring visuospatial dysfunction in schizophrenia.

Arch Gen Psychiatry. 2006;63:731-740

Author Affiliations:
Department of Psychiatry, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City (Drs Ho, O'Leary, Andreasen, and Wassink and Ms Librant); and Department of Psychiatry, University of Minnesota Medical School, Minneapolis (Dr Milev).

SCHIZOPHRENIA IS A COMPLEX genetic disorder characterized clinically by a heterogeneous syndrome comprising delusions, hallucinations, and cognitive impairment. These signs and symptoms arise from dysfunction in distributed neural circuits and from complex gene-environment interactions. One approach toward tackling the complex genetics and phenotypic heterogeneity[1,2] has been to better understand the genetic basis of cognitive impairment, a core endophenotypic feature of schizophrenia. Using a large cohort of patients with schizophrenia and healthy volunteers, our study pursues this research by investigating the phenotypic correlates (cognition and magnetic resonance [MR] imaging [MRI] brain gray matter [GM] volumes) of a single nucleotide polymorphism (SNP) within the brain-derived neurotrophic factor (BDNF) gene.

Brain-derived neurotrophic factor, a vital trophic protein for neuronal survival and differentiation in the developing ner-

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

vous system, is also important in modulating activity-dependent synaptic plasticity among mature neurons.[3,4] Stimulation of hippocampal and visual cortical neurons increases BDNF gene transcription, protein secretion, and synaptic signaling. Activity-dependent BDNF secretion is required for long-term potentiation and long-term depression, which are cellular mechanisms underlying learning and memory.[5,6] The role of BDNF in cognition is further supported by studies[7,8] of BDNF-mutant mice that show hippocampal-dependent learning deficits and impaired pattern discrimination.

Recent studies[9-12] indicate that a SNP (rs6265) producing a valine (Val)–to–methionine (Met) substitution in the proBDNF protein at codon 66 (Val66Met) is related to hippocampus-mediated memory performance in humans. Hippocampal neurons transfected with the $BDNF_{Met}$ variant show less depolarization-induced BDNF secretion.[9,13] It is postulated that Met substitution leads to inefficient trafficking of BDNF to secretory granules, reduced activity-dependent BDNF release, and in turn, poorer hippocampus-mediated memory. Thus, Met allele carriers, regardless of whether they are healthy human volunteers, probands with schizophrenia, or their unaffected siblings, have poorer episodic memory than their respective Val-homozygous counterparts.[9,11,12] Heterozygotes also have significantly lower left hippocampal *N*-acetyl aspartate levels.[9] Healthy volunteers who are Met allele carriers have lower hippocampal functional MRI blood oxygenation level–dependent response while performing a declarative memory task[10] and have smaller hippocampal and prefrontal GM volumes.[14,15]

Thus, the BDNF Val66Met polymorphism appears to be important in hippocampus-dependent memory in humans, possibly regardless of schizophrenia affectation status. However, to our knowledge, its effects on other cognitive domains in healthy individuals have not been systematically studied. Whether this functional SNP has a specific role in conferring cognitive dysfunction in schizophrenia is also unknown. Therefore, we characterized the neurocognitive phenotype of the BDNF Val66Met polymorphism by assessing the genotype effects on the scores on a comprehensive battery of standardized neuropsychological tests and on MRI GM brain volumes. Since larger GM volumes in specific brain regions have been associated with better performance in different cognitive domains,[16] using these 2 complementary approaches will provide convergent evidence regarding genotype-phenotype relationships.

METHODS

SUBJECTS

Two hundred ninety-three patients with schizophrenia spectrum disorders and 144 healthy volunteers were obtained through the University of Iowa Mental Health Clinical Research Center, Iowa City. These subjects have participated in various research studies at the Mental Health Clinical Research Center that were approved by the University of Iowa institutional review board. All of the subjects gave written informed consent to undergo research assessments. Patients were evaluated using a semistructured interview instrument, the Comprehensive Assessment of Symptoms and History,[17] from which schizophrenia (n=264), schizoaffective disorder (n=23), or schizotypal personality disorder (n=6) diagnoses meeting *DSM-III-R* or *DSM-IV* criteria were based. Healthy volunteers were recruited from the community through newspaper advertisements. They were initially screened by telephone and further evaluated using an abbreviated version of the Comprehensive Assessment of Symptoms and History to exclude subjects with current or past medical, neurological, or psychiatric illnesses.

GENETIC ANALYSES

The DNA was prepared by high-salt extraction from whole blood.[18] The BDNF Val66Met genotyping was performed using the fluorogenic 5′ nuclease method (TaqMan; Applied Biosystems, Foster City, Calif) using reagents including VIC- and FAM-labeled probes as well as TaqMan Universal PCR Master Mix (Applied Biosystems). Polymerase chain reaction and allele calling were performed on an Mx3000P QPCR thermocycler (Stratagene, La Jolla, Calif). Replicate samples were included on all of the genotyping plates to ensure accurate allele calling.

NEUROCOGNITIVE ASSESSMENT

All of the study subjects were administered a comprehensive cognitive battery by psychometrists who have been trained in standardized assessment and scoring procedures. Testing generally took approximately 4 hours to complete and, when necessary, occurred over several sessions.

To provide comprehensive yet efficient assessment of the relationships between cognitive performance and the BDNF polymorphism, the neuropsychological tests were grouped into cognitive domains on the basis of a priori theoretical considerations.[19-23] These 5 domains were verbal memory, processing speed or attention, problem solving, language skills, and visuospatial skills. These theoretical groupings of cognitive domains have good internal consistency, and their internal reliability has been tested using Cronbach α.[19,24] The median Cronbach α for the 5 cognitive domains was 0.80 (range, 0.75-0.85).

The verbal memory domain comprises the following neuropsychological tests: Rey Auditory Verbal Learning Test trials 1 through 5, Rey Auditory Verbal Learning Test trial 7, Rey Auditory Verbal Learning Test delayed recall subtest, Wechsler Memory Scale–Revised logical memory immediate recall subtest, and Wechsler Memory Scale–Revised logical memory delayed recall subtest. The component neuropsychological tests for visuospatial skills were the Rey-Osterrieth Complex Figure Test copy subtest, Wechsler Adult Intelligence Scale–Revised (WAIS-R) block design subtest, WAIS-R object assembly subtest, and Benton Judgment of Line Orientation test. The remaining 3 cognitive domains, computed using 18 other neuropsychological test variables, have been previously described.[19]

Prior to deriving cognitive domain scores for subjects in this study, the raw test score from each of the neuropsychological test variables was converted to a *z* score (mean [SD] *z* score, 0 [1]) based on norms established using our database of 576 healthy volunteers. Since these almost 600 healthy volunteers were recruited from the same geographical area and were tested by the same psychometrists, our normative data set provides a consistent and uniform basis for deriving the *z* scores. Scores were reversed where necessary so that a larger negative score indicates poorer performance below the mean. Using these *z* scores, each domain score is the summed average of the scores on its component neuropsychological test variables.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

MRI ACQUISITION AND IMAGE PROCESSING

Magnetic resonance images of the whole brain were obtained on a 1.5-T GE Signa MR scanner (General Electric Medical Systems, Milwaukee, Wis). Three different MR sequences were acquired for each subject (ie, T1-weighted spoiled gradient recalled acquisition in the steady state, proton density–weighted, and T2-weighted images). The images were processed using the locally developed Brain Research: Analysis of Images, Networks, and Systems software package.[25] The imaging parameters as well as detailed descriptions of image analysis methods for measuring lobar GM volumes have been provided elsewhere.[26-29]

In brief, the T1-weighted images were spatially normalized and resampled so that the anteroposterior axis of the brain was realigned parallel to the anteroposterior commissure line, and the interhemispheric fissure was aligned on the other 2 axes. The T2- and proton density–weighted images were aligned to the spatially normalized T1-weighted image using an automated image registration program.[30] These images were then subjected to a linear transformation into standardized stereotaxic Talairach atlas space[31] to generate automated measurements of frontal, temporal, parietal, and occipital lobes, cerebellum, and subcortical regions.[28] To further classify tissue volumes into GM, white matter, and cerebrospinal fluid, we used a discriminant analysis method of tissue segmentation based on automated training class selection that used data from the T1-, T2-, and proton density–weighted sequences.[29] In this study, we examined GM volumes in the frontal, temporal, parietal, and occipital lobes.

A second set of image analysis used a voxel-based morphometry (VBM) approach to estimate GM brain volumes. The VBM approach is a whole-brain method that involves voxel-wise statistical inference about regional GM concentration or volume in relation to group membership or other variables of interest. The VBM analysis was implemented on a Linux workstation that runs Matlab 6.5, R13 (The MathWorks, Inc, Natick, Mass) to host the statistical parametric mapping package (SPM2; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). Voxel-based morphometry was performed as described by Good et al.[32] This optimized VBM method is based on the previously described VBM protocol[33] with some modifications that include the creation of study-specific templates and a modulation step. The T1-weighted MRIs were first registered and spatially normalized to the default statistical parametric mapping T1-weighted template to create study-specific templates for the groups of control subjects and patients with schizophrenia. After tissue segmentation, the study-specific templates consisted of an average T1-weighted image and a priori probability GM, white matter, and cerebrospinal fluid images. The T1-weighted images of patients with schizophrenia and control subjects were then registered and spatially normalized to the study-specific templates created in the previous step, and these warped images were segmented into GM, white matter, and cerebrospinal fluid. Only the GM images were used for the statistical analyses. The spatial normalization step involved both linear and nonlinear transformations. As a result of the nonlinear transformations, the volumes of certain brain regions may grow whereas others may shrink. The modulation step multiplies the image intensity at each voxel by the corresponding Jacobean determinant derived from the nonlinear normalization step. This modulation step effectively converts the concentration (relative amount of GM in each voxel) to absolute amounts (volumes) of GM in a voxel. Finally, the normalized modulated GM images were smoothed with a 12-mm full-width half-maximum isotropic Gaussian kernel. The modulated smoothed GM image data were used for statistical analysis with SPM2 using the framework of the general linear model.[34]

STATISTICAL ANALYSES

The BDNF Val66Met allele and genotype frequencies were compared between patients with schizophrenia and healthy volunteers using χ^2 tests. Both heterozygotes and Met homozygotes have been previously associated with impaired BDNF secretion.[9,13] Furthermore, in our sample of patients with schizophrenia and healthy volunteers, heterozygotes and Met homozygotes did not differ significantly with regard to cognitive domain scores ($t_{109} \leq 1.15$, $P \geq .25$ among patients with schizophrenia; $t_{47} \leq 1.00$, $P \geq .32$ among healthy volunteers) or lobar GM volumes ($t_{73} \leq 0.70$, $P \geq .49$ among patients with schizophrenia; $t_{21} \leq 1.14$, $P \geq .27$ among healthy volunteers). Thus, heterozygotes and Met homozygotes were combined and categorized as the Met BDNF group. The Val homozygotes were categorized as the Val BDNF group.

Analyses of the relationships between BDNF grouping and the 5 cognitive domain scores were performed using analyses of covariance. By summarizing our neuropsychological battery into cognitive domains and by performing the statistical analyses in 2 steps, we limit type I errors and reduce capitalizing on chance associations. The first step involved an analysis of covariance for each cognitive domain as the dependent variable. Each model included 6 factors: age, sex, full-scale IQ, diagnostic grouping, genotype grouping, and a diagnostic group × genotype interaction term. Main effects, ie, remaining variance after accounting for the other 5 factors in the model, for diagnostic grouping, genotype grouping, and diagnostic group × genotype interaction are presented. The diagnostic group × genotype interaction term in the model detects the differential effects that alleles might have on cognitive scores between diagnostic groups. For cognitive domains where the analysis of covariance had significant genotype main effects, a second step of follow-up analyses was then performed using the component neuropsychological test scores.

The main effects of the BDNF genotype on lobar GM volumes were also analyzed using analyses of covariance. In each general linear model, the respective lobar GM measure was the dependent measure. Intracranial volume, age, sex, diagnostic grouping, genotype grouping, and diagnostic group × genotype interaction were entered as factors into each model. The VBM statistical analyses, which also used the framework of general linear models, were performed using SPM2.[34]

RESULTS

Sociodemographic characteristics of the sample are summarized in **Table 1**. Healthy volunteers and patients with schizophrenia were of comparable age. A significantly greater proportion of patients with schizophrenia were male. Patients with schizophrenia also had fewer years of education and lower full-scale IQ scores. However, parental educational attainment was comparable between the diagnostic groups.

The BDNF allele and genotype frequencies are summarized in Table 1. The Met allele frequency was not statistically significant across diagnostic groups. Genotype distributions in healthy volunteers and patients with schizophrenia did not deviate from Hardy-Weinberg expectations (χ^2=0.35 and 0.76, respectively; $P \geq .35$).

The mean (SD) age at illness onset among patients was 21.50 (6.74) years, and the mean (SD) duration of illness was 6.70 (6.75) years. The Met and Val patient groups did not differ significantly with respect to age at illness onset, premorbid social adjustment, or severity of

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

Table 1. Sociodemographic Characteristics and Brain-Derived Neurotrophic Factor Allele and Genotype Distributions in Healthy Volunteers and Patients With Schizophrenia

Variable	Healthy Volunteers	Patients With Schizophrenia	Statistic (*P* Value)*
Subjects, No.	144	293	NA
Male, %	45.1	72.7	31.7 (<.001)
Age, mean (SD), y	27.90 (8.19)	27.39 (9.21)	0.56 (.58)
Education, mean (SD), y	15.00 (1.79)	12.87 (2.19)	10.1 (<.001)
Parental education, mean (SD), y	13.44 (2.14)	13.41 (2.57)	0.14 (.89)
Full-scale IQ, mean (SD)	110.41 (11.66)	91.49 (13.49)	14.4 (<.001)
Allele frequency, %			
Met	19.1	20.8	0.35 (.55)
Val	80.9	79.2	
Genotype frequency, No. (%)			
Met/Met	6 (4.2)	11 (3.8)	0.54 (.77) for healthy volunteers; 0.26 (.88) for patients with schizophrenia†
Met/Val	43 (29.9)	100 (34.1)	
Val/Val	95 (65.9)	182 (62.1)	

Abbreviations: Met, methionine; NA, not applicable; Val, valine.
*The values are expressed as χ^2 statistics for categorical measures and *t* statistics for continuous measures.
†Hardy-Weinberg expectations.

Table 2. Comparison of Full-Scale IQ and Cognitive Domain Scores by Diagnostic and Genotype Groupings

	z Scores for Healthy Volunteers, Mean (SD)		*z* Scores for Patients With Schizophrenia, Mean (SD)			
Neurocognitive Domain	Met (n = 49)	Val (n = 95)	Met (n = 111)	Val (n = 182)	Genotype, $F_{1,436}$ (*P* Value)*	Genotype × Diagnosis, $F_{1,436}$ (*P* Value)*
WAIS-R FSIQ	110.9 (12.9)	110.2 (11.0)	91.9 (14.5)	91.3 (12.9)	0.42 (.52)	0.07 (.78)
Verbal memory	0.03 (0.80)	0.19 (0.75)	−1.38 (1.04)	−1.31 (0.95)	4.51 (.03)	0.00 (.95)
Processing speed or attention	0.07 (0.75)	0.13 (0.60)	−1.31 (1.12)	−1.20 (0.99)	2.77 (.10)	0.64 (.42)
Problem solving	0.06 (0.52)	−0.05 (0.56)	−1.20 (1.24)	−1.23 (1.03)	0.23 (.63)	0.55 (.46)
Language	0.01 (0.89)	−0.02 (0.77)	−1.10 (1.36)	−1.24 (1.10)	0.10 (.75)	0.97 (.33)
Visuospatial abilities	0.07 (0.70)	0.04 (0.64)	−1.14 (1.55)	−0.77 (1.14)	4.12 (.04)	5.58 (.02)

Abbreviations: FSIQ, full-scale IQ; Met, methionine/methionine or methionine/valine genotype; Val, valine homozygous; WAIS-R, Wechsler Adult Intelligence Scale–Revised.
*Main effects on cognitive domain scores.

positive symptoms ($t_{291} \leq 0.89$, $P \geq .37$). The patients with schizophrenia who were carrying the Met allele had significantly fewer severe negative symptoms than the Val-homozygous patients (mean [SD] symptom severity, 10.93 [3.99] vs 11.84 [3.63], respectively; $t_{291}=2.00$, $P=.02$).

GENOTYPE EFFECTS ON COGNITIVE DOMAIN SCORES

The effects of the BDNF Val66Met polymorphism on full-scale IQ scores and on the 5 neurocognitive domains are summarized in **Table 2**. There were significant genotype effects on verbal memory performance ($F_{1,436}=4.51$, $P=.03$) and on visuospatial abilities ($F_{1,436}=4.12$, $P=.04$). No statistically significant genotype effects or genotype × diagnosis effects were observed with regard to full-scale IQ, processing speed or attention, problem solving, or language cognitive domain scores.

Healthy volunteers who were Val homozygous had higher verbal memory cognitive domain scores than healthy volunteers carrying the Met allele. Similarly, the mean verbal memory score in patients with schizophrenia who were Val homozygous was also higher than in the Met patient group. In addition to a significant genotype effect, there was also a statistically significant genotype × diagnosis effect on visuospatial abilities (Table 2) ($F_{1,436}=5.58$, $P=.02$). Patients with the Met allele were significantly more impaired than patients who were Val homozygous ($F_{1,292}=10.46$, $P=.001$). There were, however, no group differences in visuospatial performance among healthy volunteers ($F_{1,143}=0.27$, $P=.61$).

Approximately one third of patients with schizophrenia were not receiving antipsychotic treatment at the time of neurocognitive testing (33 patients were antipsychotic naïve and 59 patients had been noncompliant or had undergone a medication washout prior to functional neuroimaging studies). Almost half of the patients were treated with the newer atypical antipsychotic medications (132 patients received monotherapy and 9 patients received a newer atypical medication plus a typical antipsychotic medication); 23 patients received typical antipsychotic monotherapy and 37 patients required clozapine treatment. The BDNF genotype frequency did not differ significantly across antipsychotic treatment groups ($\chi^2_2=0.70$, $P=.70$). Anti-

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

Table 3. Comparison of Verbal Memory and Visuospatial Neuropsychological Tests by Diagnostic and Genotype Groupings

Component Neuropsychological Test	*z* Scores for Healthy Volunteers, Mean (SD)		*z* Scores for Patients With Schizophrenia, Mean (SD)		Genotype, $F_{1,436}$ (*P* Value)*
	Met	Val	Met	Val	
Verbal memory domain					
RAVLT trials 1-5	−0.01 (1.03)	0.14 (0.87)	−1.64 (1.31)	−1.50 (1.15)	5.80 (.02)
RAVLT trial 7	0.01 (1.07)	0.03 (0.92)	−1.41 (1.36)	−1.35 (1.15)	1.40 (.24)
RAVLT delayed recall subtest	0.02 (1.05)	0.03 (0.94)	−1.48 (1.20)	−1.30 (1.13)	3.85 (.05)
WMS-R logical memory immediate recall subtest	−0.03 (0.78)	0.25 (0.92)	−1.26 (1.11)	−1.23 (1.14)	4.57 (.03)
WMS-R logical memory delayed recall subtest	0.03 (0.79)	0.28 (0.82)	−1.07 (1.04)	−1.13 (1.03)	2.72 (.09)
Visuospatial abilities domain					
ROCFT copy subtest	0.05 (0.79)	0.16 (0.77)	−1.33 (2.55)	−0.99 (1.95)	3.60 (.05)
WAIS-R block design subtest	0.00 (1.04)	0.02 (0.95)	−0.12 (1.46)	−0.84 (1.32)	6.33 (.01)
WAIS-R object assembly subtest	0.04 (1.00)	0.02 (0.88)	−0.91 (1.33)	−0.75 (1.19)	2.44 (.12)
Benton Judgment of Line Orientation	0.17 (0.88)	−0.04 (1.01)	−1.01 (2.11)	−0.48 (1.48)	4.80 (.03)

Abbreviations: Met, methionine/methionine or methionine/valine genotype; RAVLT, Rey Auditory Verbal Learning Test; ROCFT, Rey-Osterrieth Complex Figure Test; Val, valine/valine genotype; WAIS-R, Wechsler Adult Intelligence Scale–Revised; WMS-R, Wechsler Memory Scale–Revised.
*Effects covarying for sex, full-scale IQ, age, and diagnostic grouping.

psychotic treatment (treatment vs no treatment or atypical medications vs typical medications) had no significant main effects on verbal memory or visuospatial cognitive domain scores (both $P \geq .09$). When antipsychotic treatment was entered into the general linear models, the main effects of genotype remained statistically significant ($P < .05$). Details of analyses are available on request.

GENOTYPE EFFECTS ON COMPONENT NEUROPSYCHOLOGICAL TESTS WITHIN VERBAL MEMORY AND VISUOSPATIAL COGNITIVE DOMAINS

For the 2 cognitive domains in which there were significant genotype effects, the mean *z* scores for individual component neuropsychological tests, broken down by diagnostic groupings and by genotype, are summarized in **Table 3** and **Figure**, A.

Within the verbal memory cognitive domain, there were significant genotype effects on 2 of the 3 Rey Auditory Verbal Learning Test scores (mean of trials 1-5 and delayed recall) and on the Wechsler Memory Scale–Revised logical memory immediate recall subtest ($F_{1,436} \geq 3.85$, $P \leq .05$). The effects of genotype on the Wechsler Memory Scale–Revised logical memory delayed recall subtest approached but did not achieve statistical significance ($F_{1,436} = 2.72$, $P = .09$).

For the component neuropsychological tests in the visuospatial abilities domain, the BDNF genotype had significant effects on the Rey-Osterrieth Complex Figure Test copy subtest, the WAIS-R block design subtest, and the Benton Judgment of Line Orientation test ($F_{1,436} \geq 3.60$, $P \leq .05$). More interestingly, compared with Val-homozygous patients with schizophrenia, the Met patient group consistently had greater impairment in all of the 4 tests that assessed visuospatial abilities (Figure, A) (significant main effects of genotype for the WAIS-R block design subtest and the Benton Judgment of Line Orientation test: $F_{1,292} \geq 7.49$, $P \leq .007$). Among healthy volunteers, on the other hand, there were no statistically significant genotype effects on any of the 4 component neuropsychological tests used in computing the visuospatial abilities domain (Figure, A) ($F_{1,143} \leq 2.50$, $P \geq .16$).

MRI BRAIN GM VOLUME CORRELATES

Eighty healthy volunteers and 183 patients with schizophrenia received multispectral MRI brain scans. The remaining 64 healthy volunteers and 110 patients with schizophrenia did not have available MRI scans because they were claustrophobic in the scanner, had poor-quality scans, or had scans obtained using noncomparable imaging parameters (either on an older or newer scanning protocol). There were no statistically significant differences between healthy volunteers with and without MRI data or between patients with schizophrenia with and without MRI data with regard to sex composition, BDNF genotype distribution, age, clinical characteristics, or cognitive domain scores (details of statistical analyses available on request).

We first compared Talairach-based lobar GM volumes between genotype groupings. We further explored genotype effects on GM volumes from smaller brain regions using optimized VBM. There were significant genotype effects on GM volumes within brain regions known to subserve verbal memory and visuospatial abilities (**Table 4**) (temporal lobar GM: $F_{1,262} = 5.44$, $P = .02$; occipital lobar GM: $F_{1,262} = 5.73$, $P = .02$). Patients with schizophrenia and healthy volunteers who carried the Met allele had smaller temporal and occipital lobar GM volumes than their respective Val-homozygous counterparts. There were no significant genotype × group interactions on any of the lobar GM volume measures.

Since our automated Talairach-based method provides only lobar GM volumes, we further explored the

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

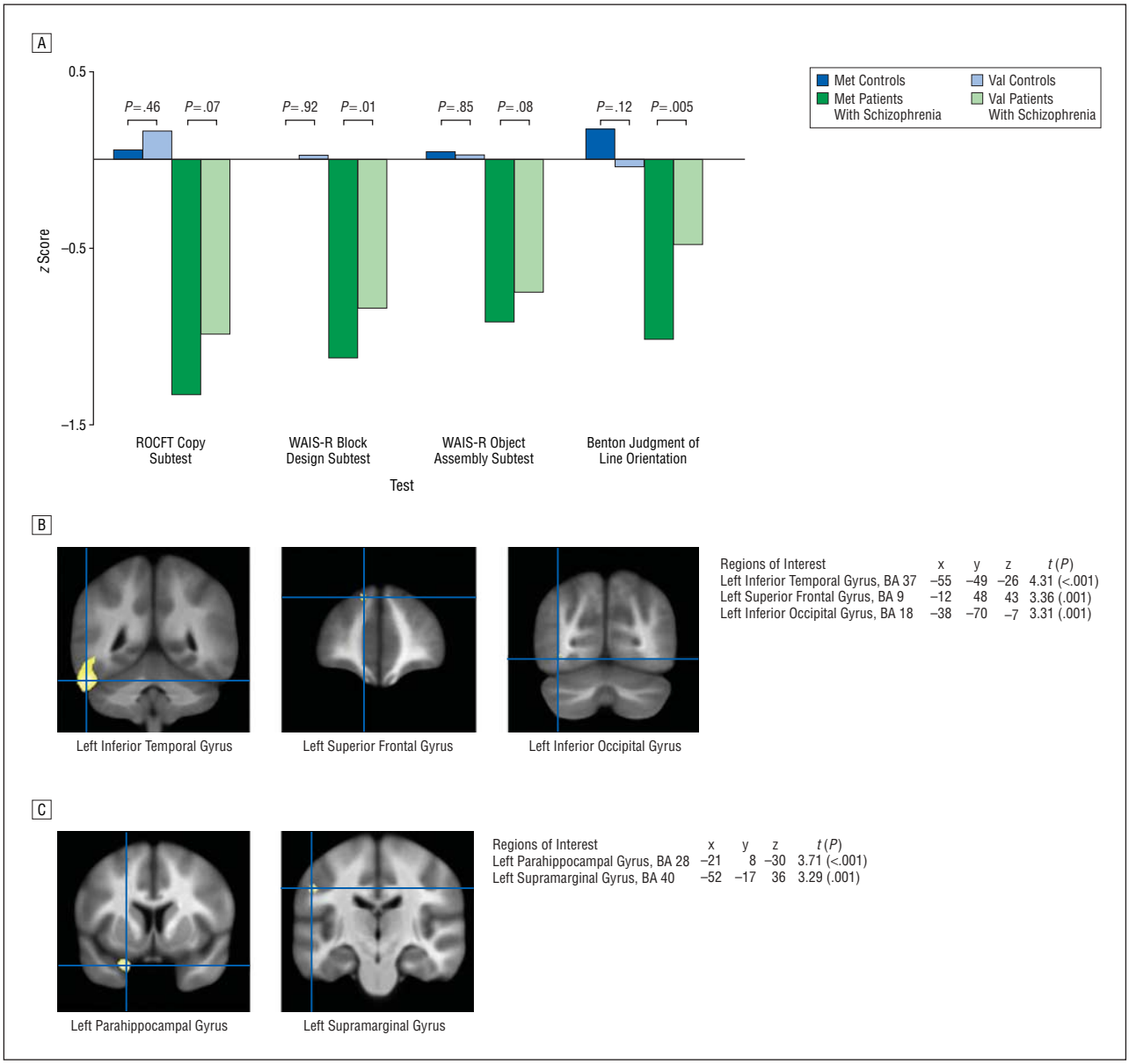

Figure. Cognitive and brain morphometric correlates of the brain-derived neurotrophic factor Val66Met gene polymorphism. A, Comparison of neuropsychological test scores (*z* scores) within visuospatial cognitive domains between genotype groupings in healthy volunteers and patients with schizophrenia (*P* values for genotype effects covarying for sex, full-scale IQ, and age). ROCFT indicates Rey-Osterrieth Complex Figure Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised; Met, methionine/methionine or methionine/valine genotype; and Val, valine/valine genotype. Optimized voxel-based morphometry analyses of healthy volunteers (B) and patients with schizophrenia (C) show brain regions in which Val homozygotes had greater gray matter volumes than carriers of the Met allele. BA indicates Brodmann area.

BDNF genotype effects using VBM. An SPM2-based implementation of VBM compared 57 Val-homozygous healthy volunteers against 23 healthy volunteers carrying the Met allele. The Val group had significantly larger GM volumes in regions that mediate verbal memory encoding (left inferior temporal gyrus, Brodmann area [BA] 37; left prefrontal cortex, BA 9) and object perception (left lateral occipital cortex or extrastriate cortex, BA 18) (Figure, B). A separate VBM analysis comparing 111 Val-homozygous patients with schizophrenia vs 72 patients with schizophrenia carrying the Met allele indicated that Val patients had significantly larger left parahippocampal (known to mediate verbal memory encoding) and left supramarginal gyral (visuomotor control) GM volumes (Figure, C).

COMMENT

In this study, we investigated the roles of BDNF in human cognition and in cognitive dysfunction among patients with schizophrenia. Using a large sample of healthy volunteers and patients with schizophrenia, we systematically examined the effects of the BDNF Val66Met gene polymorphism on the scores on a comprehensive battery of standardized neuropsychological tests and on high-resolution MRI GM brain volume measures. Besides replicating the association between the $BDNF_{Met}$ variant and poor declarative memory,[9-12,14,15] we also found the $BDNF_{Met}$ variant to correlate with reduced GM volumes within brain regions known to participate in verbal

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

Table 4. Brain-Derived Neurotrophic Factor Comparison of Magnetic Resonance Imaging Lobar Gray Matter Brain Volumes by Diagnostic and Genotype Groupings

	Brain Volumes of Healthy Volunteers, Mean (SD)		Brain Volumes of Patients With Schizophrenia, Mean (SD)			
Region of Interest	Met (n = 23)	Val (n = 57)	Met (n = 72)	Val (n = 111)	Genotype, $F_{1,262}$ (*P* Value)*	Genotype × Diagnosis, $F_{1,262}$ (*P* Value)*
Frontal GM	266.5 (34.9)	270.0 (35.5)	263.8 (37.3)	266.3 (34.1)	0.06 (.80)	0.18 (.67)
Temporal GM	154.7 (17.8)	161.0 (17.3)	155.8 (18.9)	158.2 (17.8)	5.44 (.02)	0.80 (.37)
Parietal GM	143.1 (19.2)	143.5 (16.0)	140.7 (17.9)	141.0 (16.1)	0.31 (.58)	0.23 (.63)
Occipital GM	70.4 (11.0)	73.6 (9.1)	69.3 (8.9)	72.0 (10.0)	5.73 (.02)	0.00 (.99)

Abbreviations: GM, gray matter; Met, methionine/methionine or methionine/valine genotype; Val, valine/valine genotype.
*Main effects on lobar GM volumes.

memory and visuospatial abilities.[35-37] The consonance of these cognitive and brain morphology findings suggests that the BDNF Val66Met polymorphism influences specific aspects of human cognition. Genotype status did not appear to impact general intellectual abilities or affect attention, problem solving, or language skills. Of greater potential significance, we believe, is that the $BDNF_{Met}$ variant may have a specific role for conferring visuospatial dysfunction in schizophrenia. Unlike healthy volunteers, patients with schizophrenia who carry the Met allele consistently performed worse than their Val-homozygous counterparts on all of the 4 tests of visuospatial abilities. Patients with schizophrenia who carry the Met allele also had GM brain volumetric deficits in both the ventral and dorsal visual pathways.

Neurocognitive impairment, a hallmark of schizophrenia,[38-41] is not restricted to a small subset of patients. Measurable deficits are present in 40% to 60% of patients with schizophrenia.[42] Impairment tends to be generalized and involves dysfunction in multiple cognitive domains, including visuospatial abilities.[43] A recent meta-analysis[44] found that compared with healthy volunteers, the mean effect sizes for impairment in the Benton Judgment of Line Orientation test and the WAIS-R block design subtest were 0.60 and 0.46, respectively. Such deficits in visuospatial performance have often been attributed to failures of attention or short-term visual memory.[45,46] However, impairment in the perception of visual stimuli[47] and in other early-stage processing of visual information[48-53] may also contribute to poor visuospatial abilities. Visuospatial performance is subserved by large-scale, distributed neuronal networks. Object perception involves the ventral occipitotemporal pathway whereas the dorsal occipitoparietal stream is associated with spatial information.[35,37,54,55] Therefore, brain regions that mediate visuospatial abilities include the secondary visual cortices (BA 18), inferior temporal regions (BA 37), and the parietal heteromodal association cortices.

In our study, we found that carriers of the Met allele, regardless of whether they were healthy volunteers or patients with schizophrenia, had smaller occipital and temporal lobar GM volumes than their respective Val-homozygous counterparts. Additionally, from our VBM analyses, patients with schizophrenia who carried the Met allele had a smaller left supramarginal gyral GM volume than Val-homozygous patients. Healthy volunteers, on the other hand, did not show any parietal GM volume differences across genotype groupings. Because visuospatial abilities involve widely distributed neural circuits, healthy volunteers with the $BDNF_{Met}$ variant may have sufficient cognitive reserve to compensate for deficits within the occipital and temporal lobes. Thus, without parietal GM volume deficits, healthy volunteers carrying the Met allele were able to perform comparably to their Val-homozygous counterparts in neuropsychological tests assessing visuospatial abilities. On the other hand, having deficits in both the ventral occipitotemporal and dorsal occipitoparietal visual pathways, patients with schizophrenia carrying the Met allele may be less able to compensate for global reductions in occipital and temporal lobar GM volumes. This may, in turn, translate into poorer performance on neuropsychological tests assessing visuospatial abilities.

Among its diverse functions of neuronal survival and in mediating synaptic plasticity, BDNF is also known to play important roles during the development of the visual cortex[56] as well as in modulating visual functions.[57-60] Visual experience–regulated secretion of BDNF is an essential molecular signal for normal visual cortical maturation. High levels of BDNF and TrkB messenger RNA expression have been found in the higher-order visual areas of adult macaque monkeys, which further suggests that BDNF may continue to regulate visual functions beyond neurodevelopment. Although the importance of BDNF in mediating visual cortical neuronal survival and synaptic plasticity within visual pathways is well established, how would a single nucleotide substitution in the gene encoding the proBDNF protein affect cognitive abilities and GM brain volumes?

As with other neurotrophins, the BDNF gene encodes a precursor peptide (proBDNF). During intracellular trafficking through the Golgi apparatus and trans-Golgi network, the proBDNF domain is subsequently cleaved off so that the remaining mature BDNF protein is packaged into secretory vesicles. Compared with the wild-type BDNF ($BDNF_{Val}$), there is relatively less efficient localization of mature BDNF to secretory vesicles when hippocampal neurons[9] or cerebral cortical neurons[13] have been transfected with the $BDNF_{Met}$ variant. Since proneurotrophins are important for proper folding, dimerization, and targeting of the mature neurotrophins,[61] Egan et al[9] and Chen et al[13] have postulated

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

that a substitution of Val with Met in the proBDNF may result in defective intracellular protein trafficking and may perturb BDNF synthesis. This would, in turn, lead to decreased activity-dependent BDNF secretion and impairment in hippocampus-mediated memory functions. Like other studies,[9-11,14,15] we also found the $BDNF_{Met}$ variant to be associated with poorer declarative memory and reduced temporal lobar GM volumes. Although similar expression studies[9,13] have not been performed on neurons from the visual brain regions, it is not inconceivable that the $BDNF_{Met}$ variant could cause analogous intracellular protein trafficking defects in neurons within distributed neural circuits subserving visuospatial abilities. With less BDNF available for activity-dependent secretion in neurons from all of the 3 nodes of the visuospatial neural circuits (ie, occipital, temporal, *and* parietal), patients carrying the Met allele may therefore show greater impairment in visuospatial test performance.

The mechanisms by which the $BDNF_{Met}$ variant affects GM brain volumes are not well understood. This may be mediated neurodevelopmentally through the neurotrophic effects of BDNF.[62] If the $BDNF_{Met}$ variant results in reduced BDNF synthesis, neuronal proliferation and neuronal survival may be decreased in a BDNF-deficient milieu. Besides having fewer neurons, the surviving neurons may also have small soma size and diminished dendritic growth,[63] which would further contribute to smaller gross GM brain volumes. Alternatively, the $BDNF_{Met}$ variant may influence GM brain volumes beyond neurodevelopment through modulating synaptic activity in mature neurons.[64]

To our knowledge, this is the first study showing that the effects of a common SNP on cognitive function in patients with schizophrenia may be different from those in healthy volunteers. Among SNPs known to contribute to variance in human cognition, polymorphisms in the cathecol-O-methyltransferase (*COMT*), BDNF, metobotropic glutamate receptor (*GRM3*), and disrupted-in-schizophrenia 1 (*DISC1*) genes appear to have similar effects in healthy volunteers and in patients with schizophrenia.[9,65-68] None of these previous studies have found significant genotype × diagnostic grouping effects with regard to working memory or verbal memory. Clearly, our finding that the $BDNF_{Met}$ variant may have a specific role for conferring visuospatial dysfunction in schizophrenia needs replication.

Our study is also limited by the inherent low specificity of standardized neuropsychological tests to isolate individual cognitive processes. Future studies may want to explore BDNF genotype effects on experimental cognitive tasks (eg, visual backward masking), where subprocesses within the visual information–processing stream could be better isolated. Additionally, our Talairach atlas–based MRI analyses tested hypotheses at the level of cerebral lobes and may miss smaller brain regions. We addressed the low regional specificity of Talairach-based lobar GM measurements by performing a second set of MRI analyses using optimized VBM. With our VBM analyses, we were able to replicate 2 previous studies[14,15] that examined MRI brain morphometric correlates of the BDNF Val66Met polymorphism. Pezawas et al[14] found reduced GM volumes in the prefrontal regions and smaller hippocampus volumes among healthy volunteers carrying the Met allele. Szeszko et al[15] found smaller hippocampus volumes among Met allele carriers and that the genotype effect on hippocampus volume was greater among patients with schizophrenia than in healthy volunteers. Our VBM analyses also indicate that brain regions important in verbal memory that are impacted by the $BDNF_{Met}$ variant may be different across diagnostic groups. Healthy volunteers carrying the Met allele had relatively smaller left inferior temporal and left superior frontal gyral GM volumes. Patients with schizophrenia carrying the Met allele, on the other hand, only had smaller left parahippocampal gyral GM volumes. The absence of frontal lobe GM volume differences between patient genotype groupings may be related to the complex genetics and heterogeneity of schizophrenia. Other schizophrenia susceptibility genes[69] may have greater effects on reducing the frontal lobe volume than the BDNF Val66Met polymorphism, thereby obscuring the influence of the $BDNF_{Met}$ variant on reducing the prefrontal GM volume among patients with schizophrenia. Additionally, the limitations of VBM analytic methods[70,71] and our choice of VBM analysis may have also contributed to these observed differences in brain regions associated with the Met allele across patients with schizophrenia and healthy volunteers.

Our findings of $BDNF_{Met}$ variant–associated verbal memory and visuospatial impairment may have potential treatment implications in schizophrenia. Since the greater part of persistent psychosocial impairment in patients with schizophrenia is attributable to cognitive deficits,[72] there has been increased interest in developing novel treatments that specifically target neurocognitive dysfunction.[73] It is hoped that cognition-enhancing treatments may then translate into improved social and vocational outcome for patients with schizophrenia. Thus, BDNF and its receptors (ie, tyrosine kinase receptor TrkB and p75) are potential molecular targets for developing treatments specific against cognitive dysfunction in schizophrenia. Strategies for exploiting this potential include pharmacological agents that elevate endogenous BDNF levels,[74] BDNF-mimetic peptides,[75] implantation of genetically engineered cells that produce and release BDNF, or intrathecal infusion of recombinant BDNF. Such novel treatments targeting BDNF transmission may have a small effect on enhancing cognition and could be especially beneficial for patients with schizophrenia who carry the Met allele. Although many hurdles will need to be overcome before such strategies will benefit patients clinically, it is hoped that as we gradually chip away at the genetic complexity and phenotypic heterogeneity of schizophrenia, individually tailored and biologically informed therapies of greater precision will replace our current approaches to the pharmacological treatment of schizophrenia.

Submitted for Publication: July 29, 2005; final revision received December 6, 2005; accepted December 13, 2005.
Correspondence: Beng-Choon Ho, MRCPsych, Department of Psychiatry, 2880 JPP, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52252 (beng-ho@uiowa.edu).

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

Funding/Support: This work was supported in part by grants MH68380, MH31593, MH40856, and MH43271 from the National Institute of Mental Health.
Previous Presentations: Parts of this research were presented at the 43rd American College of Neuropsychopharmacology Annual Meeting; December 14, 2004; San Juan, Puerto Rico; and the 10th International Congress on Schizophrenia Research; April 6, 2005; Savannah, Ga.

REFERENCES

1. Moldin SO. Indicators of liability to schizophrenia: perspectives from genetic epidemiology. *Schizophr Bull*. 1994;20:169-184.
2. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry*. 2005;10:40-68.
3. Lu B. BDNF and activity-dependent synaptic modulation. *Learn Mem*. 2003;10:86-98.
4. Lessmann V, Gottmann K, Malcangio M. Neurotrophin secretion: current facts and future prospects. *Prog Neurobiol*. 2003;69:341-374.
5. Aicardi G, Argilli E, Cappello S, Santi S, Riccio M, Thoenen H, Canossa M. Induction of long-term potentiation and depression is reflected by corresponding changes in secretion of endogenous brain-derived neurotrophic factor. *Proc Natl Acad Sci U S A*. 2004;101:15788-15792.
6. Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci*. 2001;2:24-32.
7. Korte M, Griesbeck O, Gravel C, Carroll P, Staiger V, Thoenen H, Bonhoeffer T. Virus-mediated gene transfer into hippocampal CA1 region restores long-term potentiation in brain-derived neurotrophic factor mutant mice. *Proc Natl Acad Sci U S A*. 1996;93:12547-12552.
8. Gorski JA, Balogh SA, Wehner JM, Jones KR. Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. *Neuroscience*. 2003;121:341-354.
9. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003;112:257-269.
10. Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J Neurosci*. 2003;23:6690-6694.
11. Dempster E, Toulopoulou T, McDonald C, Bramon E, Walshe M, Filbey F, Wickham H, Sham PC, Murray RM, Collier DA. Association between BDNF val66 met genotype and episodic memory. *Am J Med Genet B Neuropsychiatr Genet*. 2005;134:73-75.
12. Tan YL, Zhou DF, Cao LY, Zou YZ, Wu GY, Zhang XY. Effect of the BDNF Val66Met genotype on episodic memory in schizophrenia. *Schizophr Res*. 2005;77:355-356.
13. Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, Lee FS. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci*. 2004;24:4401-4411.
14. Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci*. 2004;24:10099-10102.
15. Szeszko PR, Lipsky R, Mentschel C, Robinson D, Gunduz-Bruce H, Sevy S, Ashtari M, Napolitano B, Bilder RM, Kane JM, Goldman D, Malhotra AK. Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Mol Psychiatry*. 2005;10:631-636.
16. Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *J Neurosci*. 1999;19:4065-4072.
17. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry*. 1992;49:615-623.
18. Lahiri DK, Nurnberger JI Jr. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. *Nucleic Acids Res*. 1991;19:5444.
19. Milev P, Ho BC, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry*. 2005;162:495-506.
20. Hill SK, Schuepbach D, Herbener ES, Keshavan MS, Sweeney JA. Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naive patients with schizophrenia. *Schizophr Res*. 2004;68:49-63.
21. Kareken DA, Gur RC, Mozley D, Mozley LH, Saykin AJ, Shtasel DL, Gur RE. Cognitive functioning and neuroanatomic volume measures in schizophrenia. *Neuropsychology*. 1995;9:211-219.
22. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry*. 1994;51:124-131.
23. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, Fenton WS, Frese F, Goldberg TE, Heaton RK, Keefe RS, Kern RS, Kraemer H, Stover E, Weinberger DR, Zalcman S, Marder SR. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004;56:301-307.
24. Ho BC, Alicata D, Ward J, Moser DJ, O'Leary DS, Arndt S, Andreasen NC. Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. *Am J Psychiatry*. 2003;160:142-148.
25. Magnotta VA, Harris G, Andreasen NC, O'Leary DS, Yuh WT, Heckel D. Structural MR image processing using the BRAINS2 toolbox. *Comput Med Imaging Graph*. 2002;26:251-264.
26. Andreasen NC, Cizadlo T, Harris G, Swayze V, O'Leary DS, Cohen G, Ehrhardt J, Yuh WT. Voxel processing techniques for the antemortem study of neuroanatomy and neuropathology using magnetic resonance imaging. *J Neuropsychiatry Clin Neurosci*. 1993;5:121-130.
27. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V II, O'Leary DS, Ehrhardt JC, Yuh WT. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. *JAMA*. 1994;272:1763-1769.
28. Andreasen NC, Rajarethinam R, Cizadlo T, Arndt S, Swayze VW II, Flashman LA, O'Leary DS, Ehrhardt JC, Yuh WT. Automatic atlas-based volume estimation of human brain regions from MR images. *J Comput Assist Tomogr*. 1996;20:98-106.
29. Harris G, Andreasen NC, Cizadlo T, Bailey JM, Bockholt HJ, Magnotta VA, Arndt S. Improving tissue classification in MRI: a three-dimensional multispectral discriminant analysis method with automated training class selection. *J Comput Assist Tomogr*. 1999;23:144-154.
30. Woods RP, Cherry SR, Mazziotta JC. Rapid automated algorithm for aligning and reslicing PET images. *J Comput Assist Tomogr*. 1992;16:620-633.
31. Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme Medical Publishers; 1988.
32. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*. 2001;14:21-36.
33. Ashburner J, Friston KJ. Voxel-based morphometry: the methods. *Neuroimage*. 2000;11:805-821.
34. Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp*. 1995;2:189-210.
35. Cabeza R, Nyberg L. Imaging cognition, II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci*. 2000;12:1-47.
36. Cirillo MA, Seidman LJ. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychol Rev*. 2003;13:43-77.
37. Ng VW, Bullmore ET, de Zubicaray GI, Cooper A, Suckling J, Williams SC. Identifying rate-limiting nodes in large-scale cortical networks for visuospatial processing: an illustration using fMRI. *J Cogn Neurosci*. 2001;13:537-545.
38. Kraepelin E. *Dementia Praecox and Paraphrenia*. Barclay RM, Robertson GM, trans. Edinburgh, Scotland: Livingstone; 1919.
39. Bleuler E. *Dementia Praecox or the Group of Schizophrenias*. Zinkin J, trans. New York, NY: International Universities Press; 1950.
40. Goldman-Rakic PS. Prefrontal cortical dysfunction in schizophrenia: the relevance of working memory. In: Carroll BJ, Barrett JE, eds. *Psychopathology and the Brain*. New York, NY: Raven Press; 1990:1-23.
41. Gur RC, Ragland JD, Gur RE. Cognitive changes in schizophrenia: a critical look. *Int Rev Psychiatry*. 1997;9:449-457.
42. Goldberg TE, Kelsoe JR, Weinberger DR, Pliskin NH, Kirwin PD, Berman KF. Performance of schizophrenic patients on putative neuropsychological tests of frontal lobe function. *Int J Neurosci*. 1988;42:51-58.
43. Mohamed S, Paulsen J, O'Leary D, Arndt S, Andreasen N. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch Gen Psychiatry*. 1999;56:749-754.
44. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12:426-445.
45. Nestor PG, Faux SF, McCarley RW, Shenton ME, Sands SF. Measurement of visual sustained attention in schizophrenia using signal detection analysis and a newly developed computerized CPT task. *Schizophr Res*. 1990;3:329-332.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017

46. Park S, Holzman PS. Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry*. 1992;49:975-982.
47. O'Donnell BF, Swearer JM, Smith LT, Nestor PG, Shenton ME, McCarley RW. Selective deficits in visual perception and recognition in schizophrenia. *Am J Psychiatry*. 1996;153:687-692.
48. Miller S, Saccuzzo D, Braff D. Information processing deficits in remitted schizophrenics. *J Abnorm Psychol*. 1979;88:446-449.
49. Saccuzzo DP, Braff DL. Early information processing deficit in schizophrenia: new findings using schizophrenic subgroups and manic control subjects. *Arch Gen Psychiatry*. 1981;38:175-179.
50. Knight RA, Elliott DS, Freedman EG. Short-term visual memory in schizophrenics. *J Abnorm Psychol*. 1985;94:427-442.
51. Green M, Walker E. Symptom correlates of vulnerability to backward masking in schizophrenia. *Am J Psychiatry*. 1986;143:181-186.
52. Cadenhead KS, Serper Y, Braff DL. Transient vs sustained visual channels in the visual backward masking deficits of schizophrenia patients. *Biol Psychiatry*. 1998; 43:132-138.
53. Schwartz BD, Winstead DK. Visual processing deficits in acute and chronic schizophrenics. *Biol Psychiatry*. 1982;17:1377-1387.
54. Kanwisher N, Downing P, Epstein R, Kourtzi Z. Functional neuroimaging of human visual recognition. In: Cabeza R, Kingstone A, eds. *Handbook of Functional Neuroimaging of Cognition*. Cambridge, Mass: MIT Press; 2001.
55. Potts GF, Gugino LD, Leventon ME, Grimson WE, Kikinis R, Cote W, Alexander E, Anderson JE, Ettinger GJ, Aglio LS, Shenton ME. Visual hemifield mapping using transcranial magnetic stimulation coregistered with cortical surfaces derived from magnetic resonance images. *J Clin Neurophysiol*. 1998;15: 344-350.
56. Gianfranceschi L, Siciliano R, Walls J, Morales B, Kirkwood A, Huang ZJ, Tonegawa S, Maffei L. Visual cortex is rescued from the effects of dark rearing by overexpression of BDNF. *Proc Natl Acad Sci U S A*. 2003;100: 12486-12491.
57. Jiang B, Kitamura A, Yasuda H, Sohya K, Maruyama A, Yanagawa Y, Obata K, Tsumoto T. Brain-derived neurotrophic factor acutely depresses excitatory synaptic transmission to GABAergic neurons in visual cortical slices. *Eur J Neurosci*. 2004;20:709-718.
58. Desai NS, Rutherford LC, Turrigiano GG. BDNF regulates the intrinsic excitability of cortical neurons. *Learn Mem*. 1999;6:284-291.
59. Berardi N, Maffei L. From visual experience to visual function: roles of neurotrophins. *J Neurobiol*. 1999;41:119-126.
60. Okuno H, Tokuyama W, Li YX, Hashimoto T, Miyashita Y. Quantitative evaluation of neurotrophin and trk mRNA expression in visual and limbic areas along the occipito-temporo-hippocampal pathway in adult macaque monkeys. *J Comp Neurol*. 1999;408:378-398.
61. Rattenholl A, Lilie H, Grossmann A, Stern A, Schwarz E, Rudolph R. The prosequence facilitates folding of human nerve growth factor from *Escherichia coli* inclusion bodies. *Eur J Biochem*. 2001;268:3296-3303.
62. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci*. 2001;24:677-736.
63. Gorski JA, Zeiler SR, Tamowski S, Jones KR. Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. *J Neurosci*. 2003; 23:6856-6865.
64. Xu B, Zang K, Ruff NL, Zhang YA, McConnell SK, Stryker MP, Reichardt LF. Cortical degeneration in the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor TrkB. *Neuron*. 2000;26: 233-245.
65. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98:6917-6922.
66. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry*. 2003;60:889-896.
67. Egan MF, Straub RE, Goldberg TE, Yakub I, Callicott JH, Hariri AR, Mattay VS, Bertolino A, Hyde TM, Shannon-Weickert C, Akil M, Crook J, Vakkalanka RK, Balkissoon R, Gibbs RA, Kleinman JE, Weinberger DR. Variation in GRM3 affects cognition, prefrontal glutamate, and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2004;101:12604-12609.
68. Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR, Verchinski BA, Meyer-Lindenberg A, Balkissoon R, Kolachana B, Goldberg TE, Weinberger DR. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2005;102:8627-8632.
69. Addington AM, Gornick M, Duckworth J, Sporn A, Gogtay N, Bobb A, Greenstein D, Lenane M, Gochman P, Baker N, Balkissoon R, Vakkalanka RK, Weinberger DR, Rapoport JL, Straub RE. GAD1 (2q31.1), which encodes glutamic acid decarboxylase (GAD(67)), is associated with childhood-onset schizophrenia and cortical gray matter volume loss. *Mol Psychiatry*. 2005;10:581-588.
70. Bookstein FL. "Voxel-based morphometry" should not be used with imperfectly registered images. *Neuroimage*. 2001;14:1454-1462.
71. Davatzikos C. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *Neuroimage*. 2004;23:17-20.
72. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry*. 1996;153:321-330.
73. Marder SR, Fenton W. Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. *Schizophr Res*. 2004; 72:5-9.
74. Goff DC, Leahy L, Berman I, Posever T, Herz L, Leon AC, Johnson SA, Lynch G. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. *J Clin Psychopharmacol*. 2001;21:484-487.
75. O'Leary PD, Hughes RA. Design of potent peptide mimetics of brain-derived neurotrophic factor. *J Biol Chem*. 2003;278:25738-25744.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 01/16/2017