*Difficulty concentrating due to hypersensitivity to environmental noises*

- *Question*: How often in the past month have you had difficulty concentrating while reading or studying because of environmental noises that bothered you?
- *Answer*: (0) never, (1) rarely, (2) often, (3) always

Other variables

*Alcohol*

- *Question*: Have you drunk any alcoholic beverages within the past month?
- *Answer*: (0) not at all, (1) once or more

*Smoking*

- *Question*: Have you smoked any cigarettes within the past month?
- *Answer*: (0) not at all, (1) once or more

*Recreational drugs*

- *Question*: Have you ever used any recreational drug?
- *Answer*: (0) not at all, (1) once or more

*Amount of time spent watching TV and/or using personal computers*

- *Question*: How many hours on average do you spend watching TV and/or using personal computers every day?
- *Answer*: (0) none, (1) less than one hour, (2) one to two hours, (3) two to three hours, (4) more than three hours

*Being bullied*

- *Question*: Have you been the victim of bullying within the past year?
- *Answer*: (0) no, (1) yes

*Violence from adults in the home*

- *Question*: Within the past month, have you been the victim of violence from an adult or adults living in your household?
- *Answer*: (0) no, (1) yes

*Preference for being alone or with others*

- *Question*: Do you prefer being alone or being with others?
- *Answer*: (1) being alone, (2) being with others

*The number of people you can confide in*

- *Question*: How many people do you know that you can confide in about your worries and problems?
- *Answer*: (0) none, (1) one, (2) two, (3) three, (4) four or more

*Current contact with medical services*

- *Question*: Do you currently use any medical services to treat any disease or injury you might have?
- *Answer*: (0) no, (1) yes

## References

Adler, L.E., Gerhardt, G.A., Franks, R., Baker, N., Nagamoto, H., Drebing, C., Freedman, R., 1990. Sensory physiology and catecholamines in schizophrenia and mania. Psychiatry Res. 31, 297–309.

Arakida, M., Takahashi, S., Aoyagi, M., Kanamori, M., 2003. Examination of mental health status and related factors in junior high school students: a three-year longitudinal investigation (in Japanese). Shouni Hoken Kenkyu 62, 667–679.

Arseneault, L., Cannon, M., Murray, R., Poulton, R., Caspi, A., Moffitt, T.E., 2003. Childhood origins of violent behaviour in adults with schizophreniform disorder dagger. Br. J. Psychiatry. 183, 520–525.

Bunney, W.E., Hetrick, W.P., Bunney, B.G., Patterson, J.V., Jin, Y., Potkin, S.G., Sandman, C.A., 1999. Structured interview for assessing perceptual anomalies (SIAPA). Schizophr. Bull. 25, 577–592.

Bureau of Statistics, Ministry of Internal Affairs and Communications of Japan, 2007. Statistical Observations of Municipality (Japanese). Bureau of Statistics. Ministry of Internal Affairs and Communications, Tokyo, Japan.

Cannon, M., Walsh, E., Hollis, C., Kargin, M., Taylor, E., Murray, R., Jones, P.B., 2001. Predictors of later schizophrenia and affective psychosis among attendees at a child psychiatry department. Br. J. Psychiatry 178, 420–426.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., Zinser, M.C., 1994. Putatively psychosis-prone subjects 10 years later. J. Abnorm. Psychol. 103, 171–183.

Costello, A., Edelbrock, C., Kalas, R., Kessler, M., Klaric, S., 1982. NIMH Diagnostic Interview Schedule for Children: Child Version. National Institute of Mental Health, Rockville, MD.

D'Arcy, C., Siddique, C.M., 1984. Psychological distress among Canadian adolescents. Psychol. Med. 14, 615–628.

Davidson, M., Reichenberg, M.A., Rabinowitz, J., Weiser, M., Kaplan, Z., Mordenhai, M., 1999. Behavioral and intellectual makers for schizophrenia in apparently healthy male adolescents. Am. J. Psychiatry 156, 1328–1335.

Dhossche, D., Ferdinand, R., van der Ende, J., Hofstra, M.B., Verhulst, F., 2002. Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. Psychol. Med. 32, 619–627.

Doi, Y., Minowa, M., 2003. Factor structure of the 12-item General Health Questionnaire in the Japanese general adult population. Psychiatry Clin. Neurosci. 57, 379–383.

Done, D.J., Crow, T.J., Johnston, E.C., Sacker, A., 1994. Childhood antecedents of schizophrenia and affective illness: social adjustment at age 7 and 11. BMJ 309, 699–703.

Please cite this article as: Nishida, A., et al., Associations between psychotic-like experiences and mental health status and other psychopathologies among Japanese early teens, Schizophr. Res. (2007), doi:10.1016/j.schres.2007.11.038

Escher, S., Romme, M., Buiks, A., Delespaul, P., van Os, J., 2002. Independent course of childhood auditory hallucinations: a sequential 3-year follow-up study. Br. J. Psychiatry 181 (suppl. 43), s10–s18.

Fuchino, Y., Mizoue, T., Tokui, N., Ide, R., Fujino, Y., Yoshimura, T., 2003. Health-related lifestyle and mental health among inhabitants of a city in Japan (in Japanese). Nippon Koshu Eisei Zasshi 50, 303–313.

Fukunishi, I., 1990. The assessment of the cut-off point of the General Health Questionnaire (GHQ) in the Japanese version (in Japanese). Clinical Psychology 3, 228–234.

Goldberg, D.P., Rickels, K., Downing, R., Hesbacher, P., 1976. A comparison of two psychiatric screening tests. Br. J. Psychiatry 129, 61–67.

Hafner, H., Maurer, K., Trendler, G., Heidnen, W., Schmidt, M., Konnecke, R., 2005. Schizophrenia and depression: challenging the paradigm of two separate diseases––a controlled study of schizophrenia, depression and health controls. Schizophr. Res 77, 11–24.

Hanssen, M., Bak, M., Bijl, R., Vollebergh, W., van Os, J., 2005. The incidence and outcome of subclinical psychotic experiences in the general population. Br. J. Clin. Psychol. 44, 181–191.

Haw, C., Hawton, K., Sutton, L., Sinclair, J., Deeks, J., 2005. Schizophrenia and deliberate self-harm: a systematic review of risk factors. Suicide Life Threat. Behav. 35, 50–62.

Inskip, H.M., Harris, E.C., Barraclough, B., 1998. Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br. J. Psychiatry. 172, 35–37.

Johns, L.C., Cannon, M., Singleton, N., Murray, R.M., Farrell, M., Brugha, T., Bebbington, P., Jenkins, R., Meltzer, H., 2004. Prevalence and correlates of self-reported psychotic symptoms in the British population. Br. J. Psychiatry 185, 298–305.

Jones, P.B., Rodgers, B., Murray, R., Marmot, M., 1994. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344, 1398–1402.

Kaneita, Y., Ohida, T., Osaki, Y., Tanihata, T., Minowa, M., Suzuki, K., Wada, K., Kanda, H., Hayashi, K., 2007. Association between mental health status and sleep status among adolescents in Japan: a nationwide cross-sectional survey. J. Clin. Psychiatry 68, 1426–1435.

Kendler, K.S., Gallagher, T.J., Abelson, J.M., 1996. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample. The National Comorbidity Survey Arch. Gen. Psychiatry 53, 1022–1031.

Kim-Cohen, J., Caspi, A., Moffitt, T.E., Harrington, H., Milne, B.J., Poulton, R., 2003. Prior juvenile diagnoses in adults with mental disorders: developmental follow-back of a prospective-longitudinal cohort. Arch. Gen. Psychiatry 60, 709–717.

Lataster, T., van Os, J., Drukker, M., Henquet, C., Feron, F., Gunther, N., Myin-Germeys, I., 2006. Childhood victimisation and developmental expression of non-clinical delusional ideation and hallucinatory experiences: victimisation and non-clinical psychotic experiences. Soc. Psychiatry Psychiatr. Epidemiol. 41, 423–428.

Ludewig, S., Ludewig, K., Geyer, M.A., Hell, D., Vollenweider, F.X., 2002. Prepulse inhibition deficits in patients with panic disorder. Depress. Anxiety 15, 55–60.

Malmberg, A., Lewis, G., David, A., Allebeck, P., 1998. Premorbid adjustment and personality in people with schizophrenia. Br. J. Psychiatry 172, 308–313.

McGhie, A., Chapman, J., 1961. Disorders of attention and perception in early schizophrenia. Br. J. Med. Psychology 34, 103–116.

Mojtabai, R., 2006. Psychotic-like experiences and interpersonal violence in the general population. Soc. Psychiatry Psychiatr. Epidemiol. 41, 183–190.

Nakamura, A., 2004. Killing stoke fears over impact of net. The Japan News. http://202.221.217.59/print/news/nn062004/mn20040605a5.htm.

National Police Agency of Japan, 2005. The report of a nationwide survey of internet use among youth (Japanese). http://www.keishicho.metro.tokyo.jp/.toukei/keitai/keitai.htm.

Portzky, G., van Heeringen, K., 2007. Deliberate self-harm in adolescents. Curr. Opin. Psychiatry 20, 337–342.

Poulton, R., Caspi, A., Moffitt, T.E., Cannon, M., Murray, R., Harrington, H., 2000. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch. Gen. Psychiatry 57, 1053–1058.

Radovanovic, Z., Eric, L., 1983. Validity of the General Health Questionnaire in a Yogoslav student population. Psychol. Med. 13, 205–207.

Vandoolaeghe, E., van Hunsel, F., Nuyten, D., Maes, M., 1998. Auditory event related potentials in major depression: prolonged P300 latency and increased P200 amplitude. J. Affect. Disord. 48, 105–113.

van Os, J., 2003. Is there a continuum of psychotic experiences in the general population? Epidemiol. Psychiatr. Soc. 12, 242–252.

Verdoux, H., van Os, J., Maurice-Tison, S., Gay, B., Salamon, R., Bourgeois, M.L., 1999. Increased occurrence of depression in psychosis-prone subjects: a follow-up study in primary care settings. Compr. Psychiatry 40, 462–468.

Yung, A.R., Buckby, J.A., Cosgrave, E.M., Killackey, E.J., Baker, K., Cotton, S.M., McGorry, P.D., 2007. Association between psychotic experiences and depression in a clinical sample over 6 months. Schizophr. Res. 91, 246–253.

Please cite this article as: Nishida, A., et al., Associations between psychotic-like experiences and mental health status and other psychopathologies among Japanese early teens, Schizophr. Res. (2007), doi:10.1016/j.schres.2007.11.038

Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research 152 (2007) 261–265
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Brief report

# Phonetic mismatch negativity predicts social skills acquisition in schizophrenia

Yuki Kawakubo [a,*], Satoru Kamio [c], Takahiko Nose [a], Akira Iwanami [b], Kazuyuki Nakagome [c], Masato Fukuda [d], Nobumasa Kato [a], Mark A. Rogers [a], Kiyoto Kasai [a,*]

[a] *Department of Neuropsychiatry, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
[b] *Department of Neuropsychiatry, Graduate School of Medical Science, Tottori University Faculty of Medicine, 36 Nishi-cho, Yonago-shi, Tottori 683-8503, Japan*
[c] *Department of Medical Technology, Aino University, 3-9-25 Ohta, Ibaraki-shi, Osaka 567-0018, Japan*
[d] *Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, 3-39-22 Showa-cho, Maebashi-shi, Gunma 371-8511, Japan*

Received 31 August 2005; received in revised form 23 January 2006; accepted 10 February 2006

**Abstract**

Neurobiological mechanisms for social skills acquisition in schizophrenia remain largely unknown. We investigated whether an electrophysiological index of cognitive function predicts the degree of training-related social skills improvement in schizophrenia. Thirteen patients with schizophrenia underwent assessment of mismatch negativity (MMN) event-related potentials, followed by participation in a 3-month social skills training. Larger right frontal/temporal MMN current density values elicited by across-phoneme change were significantly associated with individual degrees of improvement in total social skills scores as assessed by a structured role play test. Although preliminary, these results suggest that phonetic MMN could be an index of social skills acquisition in patients with schizophrenia.


*Keywords:* Schizophrenia; Event-related potentials (ERPs); Mismatch negativity (MMN); Phoneme; Social skills; Cognitive

## 1. Introduction

Cognitive dysfunction is one of the core features of schizophrenia (Andreasen et al., 1999), and is more closely related to social and functional outcome than are clinical symptoms (Green, 1996). In psychiatric rehabilitation, social-skills training has been effective in improving social skills in patients with schizophrenia (Liberman et al., 1986). However, neurobiological mechanisms underlying social skills acquisition in schizophrenia remain largely unknown. Although evidence suggests that verbal memory and vigilance assessed by *neuropsychological* tests predict social skills acquisition in schizophrenia (Green, 1996), relationships between cognitive function at the *neurophysiological* level and social skills acquisition have not been investigated other than in pioneering work by our

* Corresponding authors. Tel.: +81 3 5800 9263; fax: +81 3 5800 6894.
*E-mail addresses:* yukik-tky@umin.ac.jp (Y. Kawakubo), kasaik-tky@umin.ac.jp (K. Kasai).

0165-1781/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2006.02.010

group that showed an association between event-related potential (ERP) indices of selective attention (N2b and P300) and social functioning assessed by a single-time evaluation (Ikebuchi et al., 1996; Iwanami et al., 1999; Ohno et al., 2000).

Mismatch negativity (MMN) is an ERP component elicited approximately 150–200 ms after the onset of physically deviant auditory stimuli in identical and repeated sequences (Näätänen et al., 1978), and can be an index of the process of detection of acoustic changes or auditory sensory memory in humans. Many investigators have reported a reduction in tone-MMN amplitude in schizophrenia (Shelley et al., 1991; Javitt et al., 1998; Catts et al., 1995; Hirayasu et al., 1998; Kasai et al., 1999a,b; Michie et al., 2000, although see O'Donnell et al., 1994). Recently, Kasai et al. (2002) found patients with schizophrenia showed more deficits in MMN elicited by across-phoneme change in speech sounds (i.e., change between vowels /a/ versus /o/) than phoneme- or tone-duration MMN. These results are compatible with the hypothesis that cognitive dysfunction in schizophrenia is best characterized as that in language-related function (Saykin et al., 1994; McCarley et al., 1999). Light and Braff (2005a) showed that lower tone-duration MMN amplitude was significantly associated with lower scores on global assessment of functioning in patients with schizophrenia. Thus, MMN deficits may represent a core neurophysiological dysfunction linked to global impairments in everyday functioning in schizophrenia. However, evaluation of social functioning was made at single time point, and thus whether MMN can predict social skills *acquisition* is unknown.

Accordingly, the present study aimed to investigate the relationship between MMN and degree of social skills acquisition following 3-month training in patients with schizophrenia. We predicted that across-phoneme MMN would be more tightly coupled with social skills acquisition than phoneme- or tone-duration MMN.

## 2. Method

### 2.1. Subjects

Thirteen outpatients with schizophrenia (9 males and 4 females; mean age = 27.9 [S.D. = 4.0]) were recruited from the Day-treatment Unit, Department of Neuropsychiatry, University of Tokyo, Japan. All patients had participated in our previous ERP study ($n$ = 23) (Kasai et al., 2002). All were right-handed (Edinburgh inventory; Oldfield, 1971). Diagnosis of schizophrenia was made by structured clinical interview for DSM-IV axis I disorder clinical version by one trained psychiatrist (K.K.). The mean duration of illness was 7.4 years (S.D. = 4.3), and the mean score of patients' IQ (Wechsler adult intelligence scale-revised; WAIS-R) was 89.8 (S.D. = 11.4). All of the patients received typical neuroleptics alone, the mean dose being 421.2 mg/day (chlorpromazine equivalents; S.D. = 251.9). All patients were clinically stable, and their psychiatric symptoms were evaluated by K.K. using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) before social skills training. The mean scores for positive symptoms, negative symptoms and general psychopathology were 10.8 (S.D. = 3.4), 16.8 (S.D. = 5.8), 30.5 (S.D. = 7.5), respectively. After a complete description of the study to the subjects, written informed consent was obtained.

### 2.2. ERP procedure

ERPs were recorded within 1 month before the participation in the social skills training program. Subjects were presented with auditory stimulus sequences consisting of standard stimuli ($n$ = 1080; probability = 90%) and deviant stimuli ($n$ = 120; $P$ = 10%) delivered binaurally through headphones in random order. The interstimulus interval (ISI) was 510 ± 20 ms. The subjects were instructed to watch a silent film and to ignore the stimuli.

The experiment consisted of three conditions, (1) tone-duration MMN condition (1000 Hz; 70 dB SPL; rise/fall time, 10 ms; standard, 100-ms duration; deviant, 50-ms duration), (2) phoneme-duration MMN condition (standard, Japanese vowel /a/ with a 150-ms duration; deviant, /a/ with a 100-ms duration) and (3) across-phoneme MMN condition (standard, Japanese vowel /a/ with a 150-ms duration; deviant, /o/ with a 150-ms duration). These vowel stimuli were spoken by a native-Japanese-speaking actor, digitized using the NeuroStim system (NeuroScan Inc., USA), and edited to have duration of 100 or 150 ms, loudness of 70 dB SPL and rise/fall time of 10 ms. The frequency spectra for the vowels were as follows: /a/, formant (F) 0 = 140 Hz, F1 = 760, F2 = 1250, F3 = 2750, F4 = 3600; /o/, F0 = 140 Hz, F1 = 480, F2 = 770, F3 = 2820, and F4 = 3600. The order of the three conditions was counterbalanced across the subjects.

### 2.3. ERP recording

The EEG recording procedure was described in detail elsewhere (Kasai et al., 1999a,b, 2002). Briefly, EEGs were recorded via a 128-electrode cap (Neurosoft, Inc.), referred to the tip of the nose. The analysis period was

512 ms, including a 64-ms pre-stimulus baseline. After the artifact rejection (amplitude > 50 μV, electrooculogram amplitude > 150 μV), the average waveforms were obtained separately for deviant and standard stimuli. The mean number of accepted responses was approximately 100 for all the subjects.

The MMNs were measured in difference waveforms obtained by subtracting ERPs of standard stimuli from those of deviant stimuli. The scalp current density (SCD) computation strengthens near electric fields and filters out far electric fields; thus, it is suitable for differentiating multiple generators of the activities near the cortical surface. The topographic EEG and SCD mapping methodologies employed have been described in detail elsewhere (Kasai et al., 1999a,b). Briefly, for the 104 channels in the 10–20 system the scalp potential was reconstructed by spherical spline interpolation. The SCD distributions were then obtained by computing the spatial derivatives of the spherical spline functions used in the potential map interpolation. We conducted quantitative assessment of SCD using a method similar to that proposed by Giard et al. (1990). The detailed definition was described in our previous paper (Kasai et al., 2002). Briefly described, we calculated individual SCD values for the right temporal (T) component of the tone-duration condition, and left temporal (T) and right frontal/temporal (F/T) component complex of the other two conditions. The SCD sink values were calculated by averaging values over 10–12 channels around each region.

### 2.4. Evaluation of social skills acquisition

A social skills training program was administered to patients with schizophrenia once a week for approximately 3 months. The program was provided according to the medication self-management module (Liberman, 1988). Social skills were assessed before and after the training period using a structured role play test (Ikebuchi and Anzai, 1995; Ikebuchi et al., 1996; Ohno et al., 2000). During the role play test, the subjects first viewed a scene of videotaped social interaction and were then required to indicate the problems presented in the scene, and the social goal of the scene. Responses were assessed for information receiving and processing skills. Subjects were then instructed to perform a role play with one of the testers, which was recorded on a videotape for subsequent evaluation by raters blind to individual subjects. After the role play, a tester questioned each subject to appraise his/her information-processing skills. A total of 12 parameters were evaluated. Two parameters were assessed through questioning before and after the role play: social perception and making alternative decisions. Ten parameters were assessed via videotaped role plays: eye contact, facial expression, emotional expression, voice loudness, voice tone, maintaining conversation, fluency of conversation, clarity of message, social validity of the interaction and goal attainment. A high interrater reliability between two independent raters was obtained (intraclass correlation coefficient: 0.74–0.96). The total social skills scores were calculated, and the difference between scores pre- and post-training was defined as the index of social skills acquisition.

### 2.5. Statistical analyses

The effect of social skills training was examined by paired *t*-test for social skills scores at pre- and post-training. Spearman's correlation with Bonferroni correction was used in the analyses of the relationships between social skills acquisition and five SCD values.

## 3. Results

### 3.1. Pre–post change in social skills

There was no significant difference between the social skills score post- and pre-training ($t_{1,12} = -0.325$, $P = 0.75$). This result suggests that the patients' social skills were not overall improved by the 3-month training (Table 1).

### 3.2. Correlational analysis

A significant correlation was, however, observed between social skills acquisition and right F/T SCD values under the across-phoneme condition ($r = -0.690$, uncorrected $P = 0.009$; corrected $P = 0.045$) (Fig. 1). There were no significant correlations between social

Table 1
MMN current density values and social skills scores

| | | Mean (S.D.) |
|---|---|---|
| Tone-duration MMN | Right T | −5.87 (3.6)μA/m$^3$ |
| Phoneme-duration MMN | Left T | −6.56 (4.5)μA/m$^3$ |
| | Right F/T | −3.46 (3.7)μA/m$^3$ |
| Across-phoneme MMN | Left T | −5.71 (3.2)μA/m$^3$ |
| | Right F/T | −0.27 (2.7)μA/m$^3$ |
| Social skills score | Pre-training | 150.62 (17.5) |
| | Post-training | 151.85 (21.0) |
| | Acquisition | 1.23 (13.6) |

MMN, mismatch negativity; T, temporal; F/T, frontal/temporal.

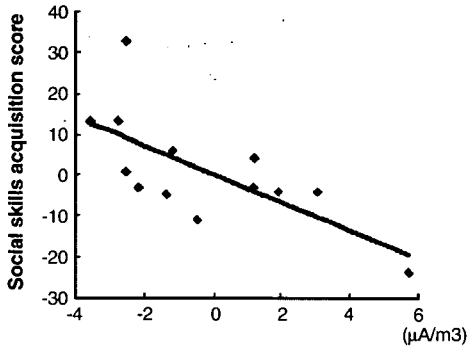


Fig. 1. Scatter plot depicting a relationship between right frontal/temporal scalp current density (SCD) values for across-phoneme mismatch negativity (MMN) and the degree of social skills acquisition in patients with schizophrenia ($n=13$).

skills acquisition and any other SCD values (corrected $P>0.21$).

## 4. Discussion

To our knowledge, this is the first study to identify a significant relationship between MMN and social skills acquisition in patients with schizophrenia. In addition, consistent with our hypothesis, MMN in response to across-phoneme change in speech sounds was more tightly associated with social skills acquisition than that in response to change in duration of a vowel or a pure tone. Kraus et al. (1998) suggested that phonetic MMN showed an increase as a result of cognitive discrimination training; thus it may be an index of language-related plasticity in the central nervous system. Our results suggest that language-related processing in schizophrenia may be a predictor for social skills acquisition in schizophrenia. The MMN-social skills acquisition relationship is important for understanding individual differences in the effectiveness of social skills training and neurobiological mechanisms underlying social skills acquisition in schizophrenia. However, this conclusion should be regarded to be tentative, since the results were derived from a small sample size and based on one significant correlation parameter. Moreover, previous studies high test–retest stability of tone-duration MMN in healthy subjects (Kathmann et al., 1999) and in schizophrenia (Light and Braff, 2005b). However, no studies including our study have investigated the stability of across-phoneme MMN in schizophrenia. To establish across-phoneme MMN as a useful metric to predict social skills acquisition, longitudinal stability should be tested in future studies.

Social skills acquisition was correlated with the right frontal/temporal SCD component in the phoneme-across condition. While the bilateral temporal components of MMN are thought to reflect auditory sensory memory function, the right frontal SCD component may reflect the automatic attention-orienting process (Giard et al., 1990) and/or the top down, modulatory control (Alho et al., 1994) to facilitate human processing of complex signals with higher information content, such as phonemes. The reason for a lack of correlation between social skills acquisition and left temporal SCD for across-phoneme MMN, which represent auditory sensory memory function for speech sounds, is not clear. One reason may be that the right SCD, a combination of temporal and frontal components, may reflect more global ability of change detection process of speech sounds than left temporal SCD.

The main limitations of our study are: (1) small sample size, (2) social skills in patients with schizophrenia were not significantly improved as the 3-month training period was too short to promote social skills as a whole. Thus, further studies using a larger sample and longer-term training will be needed.

## Acknowledgements

The authors gratefully thank Drs. Kenji Itoh and Ichiro Koshida for technical support, and Drs. Takahiro Ohno, Katsuyo Henomatsu, and Akinobu Hata for clinical assessments. This study was supported in part by Grant-in-Aid for Scientific Research for Young Investigators (No. 16790675 to KK) and by Grant-in-Aid for Scientific Research on Priority Areas (No. 17025015 to KK) from the MEXT, Japan.

## References

Alho, K., Woods, D.L., Knight, R.T., Näätänen, R., 1994. Lesions of frontal cortex diminish the auditory mismatch negativity. Electroencephalography and Clinical Neurophysiology 91, 353–362.

Andreasen, N.C., Nopoulos, P., O'Leary, D.S., Miller, D.D., Wassink, T., Flaum, M., 1999. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanism. Biological Psychiatry 46, 908–920.

Catts, S.V., Shelley, A.-M., Ward, P.B., Liebert, B., McConaghy, N., Andrews, S., Michie, P.T., 1995. Brain potential evidence for an auditory sensory memory deficit in schizophrenia. American Journal of Psychiatry 152, 213–219.

Giard, M.-H., Perrin, F., Pernier, J., Bouchet, P., 1990. Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology 27, 627–640.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? American Journal of Psychiatry 153, 321–330.

Hirayasu, Y., Potts, F., O'Donnell, B.F., Kwon, J.S., Arakaki, H., Akdag, S.J., Levitt, J.J., Shenton, M.E., McCarley, R.W., 1998. Auditory mismatch negativity in schizophrenia: topographic evaluation with a high-density recording montage. American Journal of Psychiatry 155, 1281–1284.

Ikebuchi, E., Anzai, N., 1995. Effect of the medication management module evaluated using the role play test. Psychiatry and Clinical Neurosciences 49, 151–156.

Ikebuchi, E., Nakagome, K., Tugawa, R., Asada, Y., Mori, K., Takahashi, N., Takazawa, S., Ichikawa, I., Akaho, R., 1996. What influences social skills deficits in patients with schizophrenia? Preliminary study using the role play test, WAIS-R and event-related potential. Schizophrenia Research 22, 143–150.

Iwanami, A., Yamashina, M., Kazamatsuri, H., Kamijima, K., 1999. P300 and disability of daily life in schizophrenia. Progress in Neuro-Psychopharmacology and Biological 423–430.

Javitt, D.C., Grochowski, S., Shelley, A.-M., Ritter, W., 1998. Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. Electroencephalography and Clinical Neurophysiology 108, 143–153.

Kasai, K., Nakagome, K., Itoh, K., Koshida, I., Hata, A., Iwanami, A., Fukuda, M., Hiramatsu, K.-I., Kato, N., 1999a. Multiple generators in the auditory automatic discrimination process in humans. Neuroreport 10, 2267–2271.

Kasai, K., Okazawa, K., Nakagome, K., Hiramatsu, K.-I., Hata, A., Fukuda, M., Honda, M., Miyauchi, M., Matsushita, M., 1999b. Mismatch negativity and N2b attenuation as an indicator for dysfunction of the preattentive and controlled processing for deviance detection in schizophrenia: a topographic event-related potential study. Schizophrenia Research 35, 141–156.

Kasai, K., Nakagome, K., Itoh, K., Koshida, I., Hata, A., Iwanami, A., Fukuda, M., Kato, N., 2002. Impaired cortical network for preattentive detection of change in speech sounds in schizophrenia: a high-resolution event-related potential study. American Journal of Psychiatry 159, 546–553.

Kathmann, N., Frodl-Bauch, T., Hegerl, U., 1999. Stability of the mismatch negativity under different stimulus and attention conditions. Clinical Neurophysiology 110, 317–323.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13, 261–276.

Kraus, N., McGee, T.J., Koch, D.B., 1998. Speech sound representation, perception, and plasticity: a neurophysiologic perceptive. Audiology and Neuro-Otology 3, 168–182.

Liberman, R.P., 1988. Social and independent living skills: medication-management module (Anzai, N., Ikebuchi, E., 1994. Japanese language ed. Maruzen Co. Ltd., Tokyo).

Liberman, R.P., Mueser, K.T., Wallace, C.J., 1986. Social skills training for schizophrenics at risk for relapse. American Journal of Psychiatry 143, 523–526.

Light, G.A., Braff, D.L., 2005a. Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. Archives of General Psychiatry 62, 127–136.

Light, G.A., Braff, D.L., 2005b. Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia. American Journal of Psychiatry 162, 1741–1743.

McCarley, R.W., Niznikiewicz, M.A., Salisbury, D.F., Nestor, P.G., O'Donnell, B.F., Hirayasu, Y., Grunze, H., Greene, R.W., Shenton, M.E., 1999. Cognitive dysfunction in schizophrenia: unifying basic research and clinical aspects. European Archives of Psychiatry and Clinical Neuroscience 249 (suppl 4), 69–82.

Michie, P.T., Budd, T.W., Todd, J., Rock, D., Wichmann, H., Box, J., Jablensky, A.V., 2000. Duration and frequency mismatch negativity in schizophrenia. Clinical Neurophysiology 111, 1054–1065.

Näätänen, R., Gaillard, A.W.K., M_ntysalo, S., 1978. Early selective-attention effect on evoked potential reinterpreted. Acta Psychologia 42, 313–329.

O'Donnell, B.F., Hokama, H., McCarley, R.W., Smith, R.S., Salisbury, D.F., Mondrow, E., Nestor, P.G., Shenton, M.E., 1994. Auditory ERPs to non-target stimuli in schizophrenia: relationship to probability, task demands, and target ERPs. International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology 17, 219–231.

Ohno, T., Ikebuchi, E., Henomatsu, K., Kasai, K., Nakagome, K., Hiramatsu, K., Hata, A., Fukuda, M., Honda, M., Miyauchi, M., 2000. Psychophysiological correlates of social skill deficits in persons with schizophrenia. Psychiatry Research Neuroimaging 100, 155–167.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Saykin, A.J., Shtasel, D.L., Gur, R.E., Kester, D.B., Mozley, L.H., Stafiniak, P., Gur, R.C., 1994. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Archives of General Psychiatry 51, 124–131.

Shelley, A.-M., Ward, P.B., Catts, S.V., Michie, P.T., Andrews, S., McConaghy, N., 1991. Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. Biological Psychiatry 30, 1059–1062.

ORIGINAL ARTICLE

# Progressive and Interrelated Functional and Structural Evidence of Post-Onset Brain Reduction in Schizophrenia

*Dean F. Salisbury, PhD; Noriomi Kuroki, MD, PhD; Kiyoto Kasai, MD, PhD; Martha E. Shenton, PhD; Robert W. McCarley, MD*

**Context:** Progressive brain abnormalities in schizophrenia remain controversial. Evidence of interrelated progressive functional impairment would buttress the case for structural progression. Mismatch negativity (MMN) is reduced in chronic but not first-hospitalized schizophrenia and may index progressive structural changes.

**Objective:** To determine whether MMN shows associations with underlying auditory cortex gray matter at first hospitalization and progressive reduction longitudinally.

**Design:** Cross-sectional (first hospitalization) and longitudinal (1.5-year follow-up).

**Setting:** A private psychiatric hospital.

**Participants:** Protocol entrance: MMN and magnetic resonance imaging at first hospitalization in 20 subjects with schizophrenia, 21 subjects with bipolar disorder with psychosis, and 32 control subjects. Longitudinal electrophysiologic testing: MMN in 16 subjects with schizophrenia, 17 subjects with bipolar disorder, and 20 control subjects. Longitudinal electrophysiologic testing and magnetic resonance imaging: MMN and magnetic resonance imaging in 11 subjects with schizophrenia, 13 subjects with bipolar disorder, and 13 control subjects. At each time point, reported samples were group matched for age, handedness, and parental socioeconomic status.

**Interventions:** Electrophysiologic testing and high-resolution structural magnetic resonance imaging.

**Main Outcome Measures:** Mismatch negativity amplitude and Heschl gyrus and planum temporale gray matter volumes.

**Results:** Initially, groups did not differ in MMN amplitude. Subjects with schizophrenia showed associations between MMN and Heschl gyrus ($r=-0.52$; $P=.02$) not present in the other groups. At longitudinal MMN testing, schizophrenia showed MMN reduction ($P=.004$). Only schizophrenia evinced longitudinal left hemisphere Heschl gyrus reduction ($P=.003$), highly correlated with MMN reduction ($r=0.6$; $P=.04$).

**Conclusions:** At first hospitalization for schizophrenia, MMN indexed left hemisphere Heschl gyrus gray matter volume, consistent with variable progression of prehospitalization cortical reduction. Longitudinally, the interrelated progressive reduction of functional and structural measures suggests progressive pathologic processes early in schizophrenia. An active process of progressive cortical reduction presents a potential therapeutic target. Mismatch negativity may be a simple, sensitive, and inexpensive index not only of this progressive pathologic process but also of successful intervention.

*Arch Gen Psychiatry. 2007;64:521-529*

SCHIZOPHRENIA IS A CHRONICALLY debilitating disease, typically striking during young adulthood. Approximately 50% of patients will not remain employed even part-time after their first hospitalization.[1] With the cost of treatment and care factored in, the disease has an enormous impact on society. Although most now agree that the bizarre manifestations of schizophrenia stem from brain abnormalities, disagreement about its course exists. Whether schizophrenia includes progressive brain degeneration has been controversial since Kraepelin[2] first chose the name *dementia praecox*, or precocious dementia, for the syndrome. Kraepelin conceived of an early-onset dementing disorder with progressive mental deterioration due to degeneration of the frontal and temporal neocortices. Shortly thereafter Bleuler,[3] renaming the syndrome *schizophrenia*, disagreed with invariable cognitive and structural decline, emphasizing cases with recovery. More than 100 years later, the issue has not been resolved. Whether schizophrenia involves progressive brain change is more than an esoteric issue: Progressive change presupposes an active process that can be

Author Affiliations are listed at the end of this article.

targeted pharmacologically before it has completed its insidious attack, whereas static brain lesions reflect the end stage of completed deterioration.

Evidence of prenatal and perinatal complications[4,5] and little evidence of progressive brain degeneration in chronically ill patients[6,7] have argued against a degenerative course in schizophrenia. Dominant theories of schizophrenia propose a static encephalopathy, whereby some early lesion interacts with other areas later during neurodevelopment, causing psychosis.[8] However, several lines of structural and functional evidence indicate greater-than-normal age-related cortical gray matter volume reductions in chronic schizophrenia, including greater-than-normal slowing of event-related brain potentials,[9] greater-than-normal ventricular enlargement,[10] and greater-than-normal gray matter volume reduction.[11,12] Nevertheless, studies of patients with chronic schizophrenia tested long after disease onset have not provided overwhelming evidence of progressive brain abnormalities. In contrast, magnetic resonance imaging (MRI) studies of patients early in the disease process provide greater evidence of progressive changes, including progressively increased ventricle size,[13-16] progressively reduced whole brain volume and whole gray matter,[12,17,18] and progressively reduced frontal gray matter and temporal gray matter as well as increased sulcal cerebrospinal fluid.[12,19,20] Progressive cortical gray matter loss during adolescence in childhood-onset schizophrenia has also been reported.[21,22]

Our group reported marked progressive reductions in left temporal lobe gray matter,[23,24] consistent with data from monozygotic twins discordant for schizophrenia showing marked temporal lobe reductions only in affected twins.[25] After first hospitalization, schizophrenia is characterized by progressive left hemisphere temporal lobe volume reductions. Whether the right hemisphere also shows progressive changes later in the early course of the disease is unknown, but markedly left-lateralized temporal lobe gray matter reductions remain in chronically ill patients with schizophrenia.[26] This sizable left hemisphere cortical gray matter reduction in the first few years after first hospitalization is the strongest empirical evidence of an active degenerative course in schizophrenia. This progressive cortical reduction may be nonlinear, with a circumscribed period of intense cortical reduction surrounding the first psychotic break abating after a few years.[27,28] Although the structural MRI data present strong evidence of this period of intense degeneration near symptom onset, it has been variable, and the validity of the longitudinal MRI data has been questioned, perhaps being affected by confounds such as between-image differences in brain hydration[29] or medication effects.[13,30-32]

If schizophrenia involves such a period of progressive cortical gray matter reduction near first hospitalization, then longitudinal testing of first-episode patients should reveal not only progressive reductions of brain structure but also progressive worsening of functional measures of the integrity of the shrinking cortical areas. The presence of interrelated structural and functional abnormalities, via 2 independent methods, would bolster the case for progressive cortical reduction. Auditory mismatch negativity (MMN), a bioelectric brain index of functional echoic memory processes arising mainly from the temporal lobe auditory cortex in and around Heschl gyrus,[33-36] is reduced in chronic schizophrenia[37-39] but not in first-hospitalized patients.[39] We herein provide the first prospective longitudinal evidence of interrelated progressive functional and structural brain abnormalities near schizophrenia onset, reflected in progressive voltage reduction of the MMN brain wave that is strongly correlated with progressive gray matter volume loss in the left hemisphere Heschl gyrus, which contains most, if not all, of the primary auditory cortex.[40,41]

## METHODS

### EVENT-RELATED POTENTIAL RECORDING

Event-related brain potentials were recorded from the scalp according to the method described in detail by Salisbury et al.[39] Briefly, the electroencephalogram was recorded from the scalp from 28 sites, including the standard 10-20 sites and 8 interpolated sites, passed between 0.15 and 40 Hz, and referenced to linked earlobes. Bipolar vertical electro-oculograms (above and below the right eye) and horizontal electro-oculograms (left and right canthi) were also recorded to monitor eyeblinks and movements. Activity exceeding ±50 μV at Fp1/2 or F7/8 was considered artifact and was rejected. Epochs were constructed 50 milliseconds before to 300 milliseconds after a 100-millisecond tone pip (10-millisecond rise/fall) was presented. Tones were presented 3 per second (1600 total) while subjects performed an asynchronous visual checkerboard reversal tracking task. Mismatch negativity amplitude was measured from the midline anterior site (Fz), where it is typically largest. Amplitude was quantified as the mean voltage from 100 to 200 milliseconds in the subtraction waveform constructed by removing the brain activity to standard, repetitive stimuli (1 kHz, 95%) from the brain response to rare, deviant stimuli (1.2 kHz, 5%).

### MAGNETIC RESONANCE IMAGING

Magnetic resonance images were obtained and measured according to the method described in detail by Kasai et al.[24] The primary anatomical structures of interest were the left and right Heschl gyri, containing primary and portions of secondary auditory cortices.[40,41] The planum temporale, the posterior gyrus containing secondary and tertiary auditory association cortices, was also measured bilaterally. Magnetic resonance images were obtained using a 1.5-T scanner (GE Medical Systems, Milwaukee, Wis) using 2 acquisition protocols. A 3-dimensional Fourier transform spoiled gradient-recalled acquisition protocol produced a coronal series of contiguous images (repetition time, 35 milliseconds; echo time, 5 milliseconds; repetitions, 1; nutation angle, 45°; field of view, 24 cm; number of signals acquired, 1.0; and matrix, 256×256 [192 phase-encoding steps] × 124). Voxels were 0.9375 × 0.9375 × 1.5 mm. Data were reformatted into isotropic voxels of 0.9375 mm. The second acquisition resulted in an axial series of contiguous double-echo (proton-density and T2-weighted) images used to assess intracranial contents (repetition time, 3000 milliseconds; echo time, 30 and 80 milliseconds; field of view, 24 cm; and interleaved acquisition with 3-mm slice thickness). Voxels were 0.9375 × 0.9375 × 3 mm.

### SUBJECTS

Patient recruitment and diagnostic procedures are described in detail by Salisbury et al.[39] Subjects were recruited from McLean

Hospital inpatient units at their first hospitalization for psychosis or within 1 year of their first hospitalization for psychosis (n=72; range, 0-11 months; mean, 1.7 months; and median, 2 weeks). Provisional research diagnoses were established at protocol entrance via the Structured Clinical Interview for *DSM-IV*, and diagnoses were reassessed at longitudinal testing for subjects who returned for follow-up. This was a fully longitudinal design. Subjects were tested at protocol entrance and again during the early course of their disease. Ideally, all subjects would have completed electrophysiologic and MRI retesting, but some were lost to follow-up. In addition, some subjects who completed retesting were culled to match samples. Patient sample overlap among studies is presented in **Figure 1**.

For MMN and MRI at protocol entrance, first-hospitalized patients represent a subsample of the patients reported by Salisbury et al[39] in addition to patients recruited subsequently. At protocol entrance, 16 (22%) of 72 patients refused or could not tolerate MRI. Matched first-episode patients in this analysis were tested 6 months or less from their first hospitalization (n=41; range, 0-6 months; mean, 1 month; and median, <1 week) and comprised 20 subjects with first-episode schizophrenia (3 females; mean±SD age, 24.5±6.5 years; mean±SD parental socioeconomic status [SES],[42] 1.85±0.9; with 14 receiving atypical neuroleptics, 1 receiving traditional neuroleptics, 3 receiving both, and 2 unmedicated) and 21 subjects with first-episode psychotic bipolar disorder, mania (4 females; mean±SD age, 21.8±5.0 years; mean±SD parental SES, 1.52±0.9; with 14 receiving atypical neuroleptics, 1 receiving atypical and traditional neuroleptics, and 6 receiving no antipsychotic medication). A group of 32 psychiatrically well subjects (10 females; mean±SD age, 24.1±3.7 years; mean±SD parental SES, 1.53±0.8) from the general population served as controls. Samples did not differ significantly on age, parental SES, or handedness.[43] All groups were above average in intelligence (Wechsler Adult Intelligence Scale–R[44] information subscale, group means >12). Patient samples did not differ in mean±SD overall symptom severity as measured using the Brief Psychiatric Rating Scale (BPRS)[45] (first-episode schizophrenia: 37.3±13.2; first-episode psychotic mania: 32.9±10.7; $P=.25$).

Subjects with psychosis were reassessed approximately a year and a half after protocol entrance (specific intervals are reported for each study). Subjects with psychosis lost to follow-up testing (37/72 [51%]) did not differ from retested subjects with psychosis in mean±SD age (returned: 23.3±5.4 years; lost: 25.2±7.8 years; $t_{70}=1.2$; $P=.24$), total BPRS scores (returned: 36.1±11.7; lost: 34.1±10.0; $t_{65}=0.8$; $P=.46$), medication dosages (returned: 192.4±189.1; lost: 215.4±188.3; $t_{69}=0.5$; $P>.6$), SES (returned: 3.1±1.2; lost: 3.5±1.2; $t_{67}=1.3$; $P=.20$), or parental SES (returned: 1.7±0.8; lost: 1.9±1.2; $t_{67}=0.6$; $P=.56$) measured at protocol entrance. However, subjects with psychosis lost to follow-up had lower mean±SD scaled Wechsler Adult Intelligence Scale information scores (returned: 13.4±2.7; lost: 11.5±2.9; $t_{67}=2.8$; $P=.006$), although both groups were well above average in estimated premorbid intellect. Also, subjects with psychosis lost to follow-up had worse social functioning (mean±SD Global Assessment of Functioning scale scores: returned: 37.3±8.3; lost: 31.1±8.3; $t_{66}=3.1$; $P=.003$), although both groups had major impairments in several areas of social functioning and reality testing.

All returning subjects with psychosis remained at least mildly impaired at retesting compared with premorbid functioning. Of the 35 subjects with psychosis who returned for retesting, 8 (23%) were inpatients at retesting, and 16 (46%) had been rehospitalized subsequent to protocol entrance. There were no significant differences in MMN amplitudes at retest between subjects with psychosis rehospitalized ever and those who maintained outpatient status in either patient group.

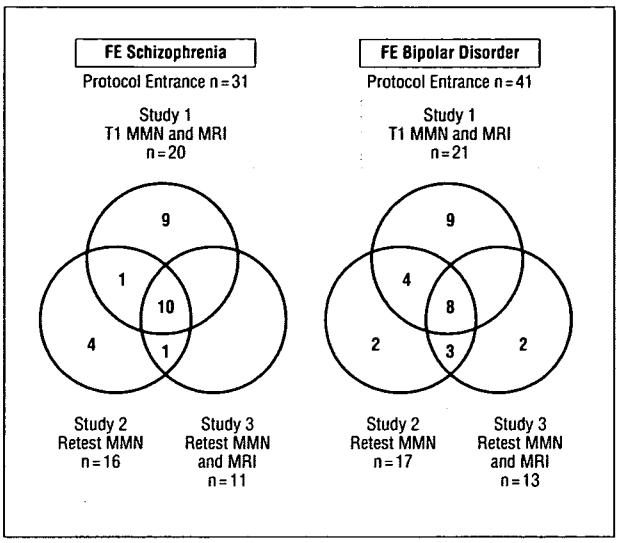


**Figure 1.** Venn diagram of the patient sample overlap among the 3 studies. FE indicates first-episode; MMN, mismatch negativity; MRI, magnetic resonance imaging; and T1, time 1.

The first comparison of longitudinal data is for MMN, which more subjects with psychosis tolerated at retest. The mean MMN retest interval did not differ significantly (subjects with schizophrenia, 1.7 years; subjects with bipolar disorder, 1.3 years; and control subjects, 1.4 years; $F_{2,50}=0.80$; $P=.46$). The matched longitudinal MMN retesting subjects with psychosis (n=33) were tested within 1 year from their first hospitalization (range, 0-11 months; mean, 1.7 months; and median, <1 week) and comprised 16 subjects with schizophrenia (3 females; mean±SD age, 26.4±8.1 years; mean±SD parental SES, 1.8±0.7) and 17 with psychotic bipolar disorder, mania (2 females; mean±SD age, 22.4±3.6 years; mean±SD parental SES, 1.5±0.7), compared with 20 psychiatrically well control subjects (4 females; mean±SD age, 24.5±4.1 years; mean±SD parental SES, 1.4±0.6). Retest electrophysiologic samples did not differ significantly on age, parental SES, or handedness.

At longitudinal retesting, 5 (14%) of 35 subjects refused or could not tolerate MRI. For combined longitudinal MMN and MRI retesting, the mean MMN retest interval did not differ significantly between groups, but there was a slight trend for subjects with bipolar disorder to have a shorter MMN retest interval (subjects with schizophrenia, 1.7 years; subjects with bipolar disorder, 1.1 years; and control subjects, 1.4 years; $F_{2,34}=2.63$; $P=.09$). The mean MRI retest interval did not differ significantly among groups (subjects with schizophrenia, 1.7 years; subjects with bipolar disorder, 1.3 years; and control subjects, 1.4 years; $F_{2,34}=0.8$; $P=.46$). The matched longitudinal MMN and MRI retesting subjects with psychosis (n=24) entered the protocol within 1 year from their first hospitalization (range, 0-11 months; mean, 2.1 months; and median, 2 weeks) and comprised 11 subjects with schizophrenia (2 females; mean±SD age, 26.0±7.9 years; mean±SD parental SES, 2.0±0.6; 4 were taking atypical medications, 4 were noncompliant, and 3 were not prescribed antipsychotic medications by their outside treaters) and 13 subjects with psychotic bipolar disorder, mania (3 females; mean±SD age, 22.1±3.3 years; mean±SD parental SES, 1.8±0.8; 7 were taking atypical medications, 3 were noncompliant, and 3 were not prescribed antipsychotic medications by their outside treaters), compared with 13 psychiatrically well control subjects (4 females; mean±SD age, 23.5±2.7 years; mean±SD parental SES, 1.4±0.7). Samples did not differ significantly on age, parental SES, or handedness.

**Table. MMN Amplitudes and Absolute MRI Volumes***

| | MMN Time 1 | MMN Time 2 | MMN Change | Left HG Time 1 | Left HG Time 2 | Left HG Change | Right HG Time 1 | Right HG Time 2 | Right HG Change |
|---|---|---|---|---|---|---|---|---|---|
| Protocol entrance | | | | | | | | | |
| Schizophrenia (n = 20) | −3.84 ± 2.54 | NA | NA | 1.61 ± 0.39 | NA | NA | 1.41 ± 0.38 | NA | NA |
| Psychotic bipolar disorder (n = 21) | −2.88 ± 1.50 | NA | NA | 1.83 ± 0.44 | NA | NA | 1.68 ± 0.50 | NA | NA |
| Controls (n = 32) | −3.82 ± 2.67 | NA | NA | 2.02 ± 0.40 | NA | NA | 1.66 ± 0.37 | NA | NA |
| MMN follow-up | | | | | | | | | |
| Schizophrenia (n = 16) | −4.25 ± 2.72 | −2.84 ± 1.89 | −1.41 ± 1.65 | NA | NA | NA | NA | NA | NA |
| Psychotic bipolar disorder (n = 17) | −3.32 ± 1.55 | −3.51 ± 2.72 | 0.19 ± 2.24 | NA | NA | NA | NA | NA | NA |
| Controls (n = 20) | −3.80 ± 1.87 | −4.18 ± 1.40 | 0.38 ± 1.50 | NA | NA | NA | NA | NA | NA |
| MMN and MRI follow-up | | | | | | | | | |
| Schizophrenia (n = 11) | −4.35 ± 2.32 | −2.90 ± 1.92 | −1.46 ± 0.94 | 1.83 ± 0.50 | 1.72 ± 0.48 | −0.113 ± 0.08 | 1.57 ± 0.51 | 1.56 ± 0.48 | −0.01 ± 0.05 |
| Psychotic bipolar disorder (n = 13) | −3.04 ± 1.20 | −3.08 ± 0.93 | 0.05 ± 1.35 | 1.78 ± 0.28 | 1.78 ± 0.28 | −0.001 ± 0.12 | 1.76 ± 0.32 | 1.73 ± 0.33 | −0.04 ± 0.08 |
| Controls (n = 13) | −4.09 ± 1.86 | −4.47 ± 1.44 | 0.39 ± 1.63 | 1.80 ± 0.37 | 1.76 ± 0.32 | −0.03 ± 0.07 | 1.86 ± 0.33 | 1.82 ± 0.34 | −0.05 ± 0.06 |

Abbreviations: HG, Heschl gyrus; MMN, mismatch negativity; MRI, magnetic resonance imaging; NA, not applicable.
*Data are given as mean ± SD.

## ANALYSES

For the analysis of MMN at protocol entrance, groups were compared using 1-way analysis of variance (ANOVA). For the analysis of relative Heschl gyrus volumes (percentage of intracranial contents) at protocol entrance, groups were compared using repeated-measures ANOVA, with hemisphere as the within-subjects factor. Associations between MMN amplitude and Heschl gyrus and planum temporale absolute gray matter volumes were assessed using Pearson correlations. Comparisons of $r$ values between groups were assessed using directional z-transforms. For longitudinal MMN testing, repeated-measures ANOVA with diagnosis as the between-subjects factor and time as a within-subjects factor tested for overall effects. Subsequently, nonparametric Wilcoxon signed rank tests were performed to assess longitudinal effects within groups. Wilcoxon signed rank tests rank the magnitudes of differences in each subject, thus preserving the ordinal magnitude of changes while also emphasizing the number of subjects showing a change. This is particularly important if significant change is driven by a subgroup of subjects: to claim that a group of patients shows progressive reductions, most, if not all, should show reduction. Pairwise $t$ tests within groups were also performed. For combined longitudinal MMN and MRI testing, repeated-measures ANOVA with diagnosis as the between-subjects factor and time as a within-subjects factor tested for overall effects on MMN and on relative Heschl gyrus volumes with the additional factor of hemisphere. Subsequently, nonparametric Wilcoxon signed rank tests and $t$ tests within groups were performed to assess longitudinal effects. To assess the associations between MMN change and absolute left hemisphere Heschl gyrus change, Pearson correlations were used. Change in MMN was calculated as follows: time 1 MMN − time 2 MMN, because MMN is a negative voltage, and Heschl change was calculated as follows: time 2 volume − time 1 volume. Thus, negative change scores mean worsening. Comparisons of $r$ values between groups were assessed using directional z-transforms. The distributions of change scores in each group were compared with random distributions using the $\chi^2$ goodness-of-fit test to determine whether groups differed from random distributions.

## RESULTS

The MMN and Heschl gyrus values for each study are given in the **Table**. Study 1 examined MMN and Heschl gyrus gray matter volumes cross-sectionally at first hospitalization for psychosis. First-hospitalized subjects with schizophrenia, first-hospitalized subjects with bipolar disorder, and psychiatrically well control subjects did not differ in MMN amplitude at initial testing ($F_{2,70}=1.2$; $P=.30$). Groups differed in relative Heschl gyrus gray matter volumes ($F_{2,70}=5.8$; $P=.005$), and all groups had larger gray matter volumes in the left hemisphere (side: $F_{1,70}=18.1$; $P<.001$). Follow-up ANOVA revealed that first-hospitalized subjects with schizophrenia had reduced relative Heschl gyrus gray matter volumes relative to controls ($F_{1,50}=11.7$; $P=.001$) and relative to first-hospitalized subjects with bipolar disorder ($F_{1,39}=6.9$; $P=.01$). Psychiatrically well controls and first-hospitalized subjects with bipolar disorder did not differ in relative Heschl gyrus gray matter volumes ($F_{1,51}=0.2$; $P=.89$). Subjects with schizophrenia showed a significant association between MMN amplitude at the mid-frontal site (where it is largest) and their left hemisphere Heschl gyrus gray matter volume ($r=-0.52$; $P=.02$) (**Figure 2**). Pairwise directional z-transform comparisons indicated that the association between MMN and left Heschl gyrus gray matter volume in first-hospitalized subjects with schizophrenia was significantly different from the association in the other groups ($P<.05$ for all). In schizophrenia, the association between MMN and left hemisphere Heschl gyrus gray matter volumes was different from the correlation in the right hemisphere (−0.18) at trend level ($P=.06$, Fisher z-transform), and no associations with the left or right planum temporale were apparent. There were no significant associations between MMN and any region of interest in the other groups. However, these cross-sectional data are only indirect evidence of an active period of brain reduction in schizophrenia near first hospitalization and can alternately be explained by variable severity of perinatal insult. Only prospective longitudinal testing from first hospitalization can definitively demonstrate a progressively worsening abnormality.

Study 2 examined MMN longitudinally. Groups did not differ in overall MMN amplitudes ($F_{2,50}=0.63$; $P=.54$). How-

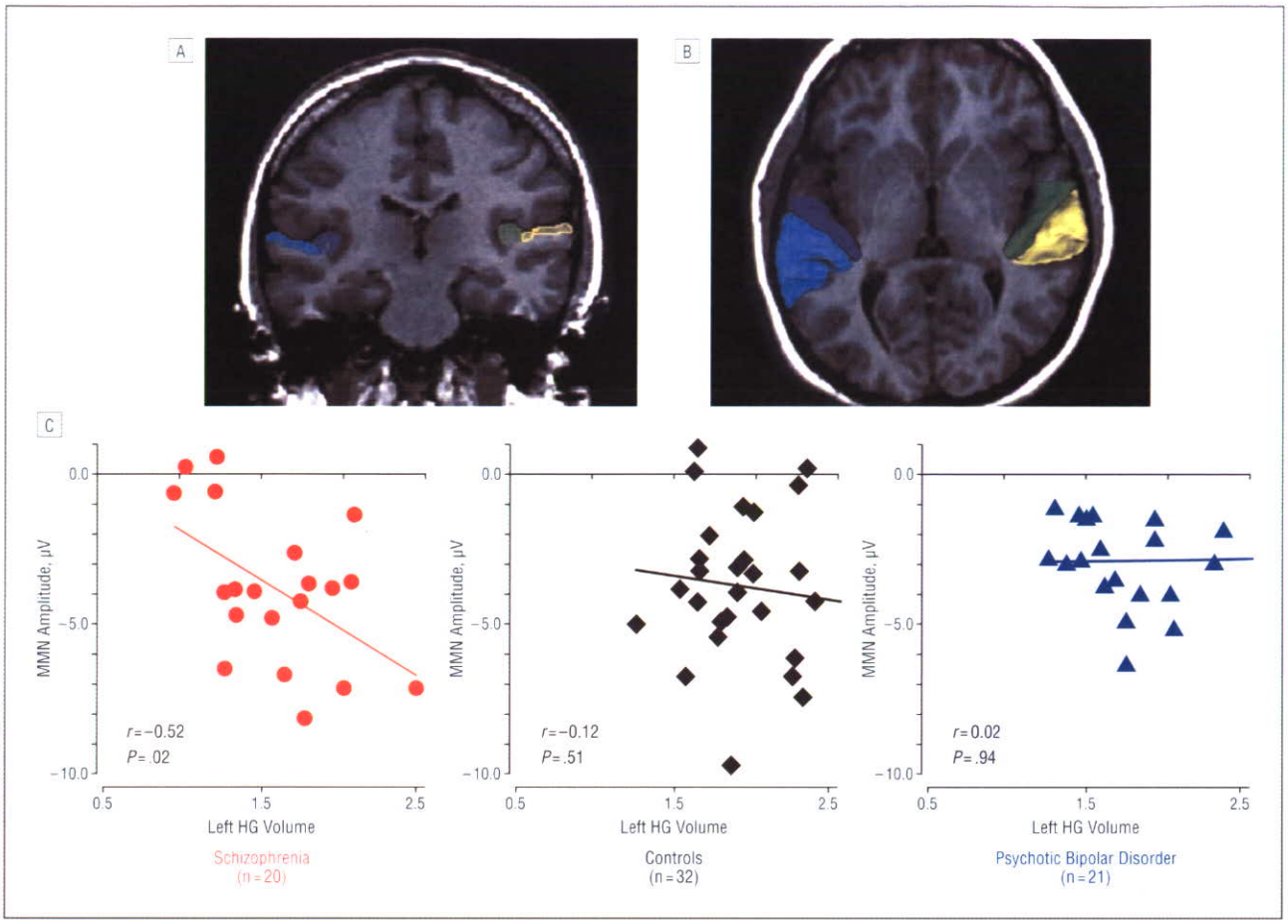


**Figure 2.** Magnetic resonance imaging–defined regions of interest and correlations with mismatch negativity (MMN) at first hospitalization.
A and B, Three-dimensional magnetic resonance imaging constructions of major subdivisions of the superior temporal plane. Heschl gyri (dark blue and dark green) mainly contain the primary auditory cortex. The planum temporale (light blue and yellow-green) contains secondary and tertiary auditory association cortices. The left side of the figure is the left hemisphere. Note the larger left hemisphere planum temporale. C, At first hospitalization, despite mean MMN amplitudes within the normal range, subjects with schizophrenia showed an abnormal relationship between MMN and underlying left hemisphere primary auditory cortex volumes, consistent with some degree of prehospitalization cortical volume reductions in some subjects with schizophrenia. HG indicates Heschl gyrus; colored lines, regression line.

ever, groups showed different changes in MMN amplitudes over time (group × time, $F_{2,50}=4.97$; $P=.01$). Only subjects with schizophrenia showed progressive reductions in MMN (**Figure 3**). Wilcoxon signed rank tests revealed that 14 of 16 subjects with schizophrenia showed smaller MMN amplitudes at retest ($Z=2.9$; $P=.004$). By contrast, 8 of 17 subjects with bipolar disorder ($Z=0.2$; $P=.83$) and 12 of 20 control subjects showed MMN reduction ($Z=0.5$; $P=.60$), essentially chance. These findings were confirmed using within-group $t$ tests, where subjects with schizophrenia showed significant MMN reductions ($t_{15}=3.4$; $P=.004$) but those with bipolar disorder ($t_{16}=0.4$; $P=.73$) and control subjects ($t_{19}=1.1$; $P=.27$) did not.

Study 3 examined subjects receiving both MMN and MRI longitudinal testing. Groups did not differ in overall MMN amplitudes ($F_{2,34}=2.16$; $P=.13$), and there were significantly different changes in MMN over time in the groups (group × time, $F_{2,34}=6.06$; $P=.006$). Wilcoxon signed rank tests revealed that 10 of 11 subjects with schizophrenia showed smaller MMN amplitudes at retest ($Z=2.8$; $P=.004$), whereas only 6 of 13 subjects with bipolar disorder ($Z=0.04$; $P=.97$) and 7 of 13 control subjects ($Z=0.5$; $P=.60$) showed MMN reduction. These findings were confirmed using within-group $t$ tests, in which subjects with schizophrenia showed significant MMN reductions ($t_{10}=5.2$; $P<.001$) but those with bipolar disorder ($t_{12}=0.12$; $P=.90$) and control subjects ($t_{12}=0.85$; $P=.41$) did not. For Heschl gyrus gray matter volumes, groups did not differ in relative gray matter volumes ($F_{2,34}=0.97$; $P=.39$), but there were significantly different changes in gray matter over time in the groups restricted to 1 hemisphere (group × hemisphere × time interaction, $F_{2,34}=4.88$; $P=.01$). Separate ANOVAs isolated the differential changes to the left hemisphere (group × time interaction, $F_{2,34}=4.52$; $P=.02$), not the right (group × time interaction, $F_{2,34}=0.86$; $P=.43$). Wilcoxon signed rank tests revealed that 11 of 11 subjects with schizophrenia showed reduction ($Z=2.9$; $P=.003$). In contrast, only 6 of 13 subjects with bipolar disorder ($Z=1.2$; $P=.25$) and 8 of 13 control subjects ($Z=0.1$; $P=.92$) showed reduction, essentially chance. These findings were confirmed using within-group $t$ tests, in which subjects with schizophrenia showed significant left Heschl gyrus gray matter reductions ($t_{10}=4.5$; $P<.001$) but those with bipolar disorder ($t_{12}=1.47$; $P=.17$) and control subjects ($t_{12}=0.05$; $P=.96$) did not.

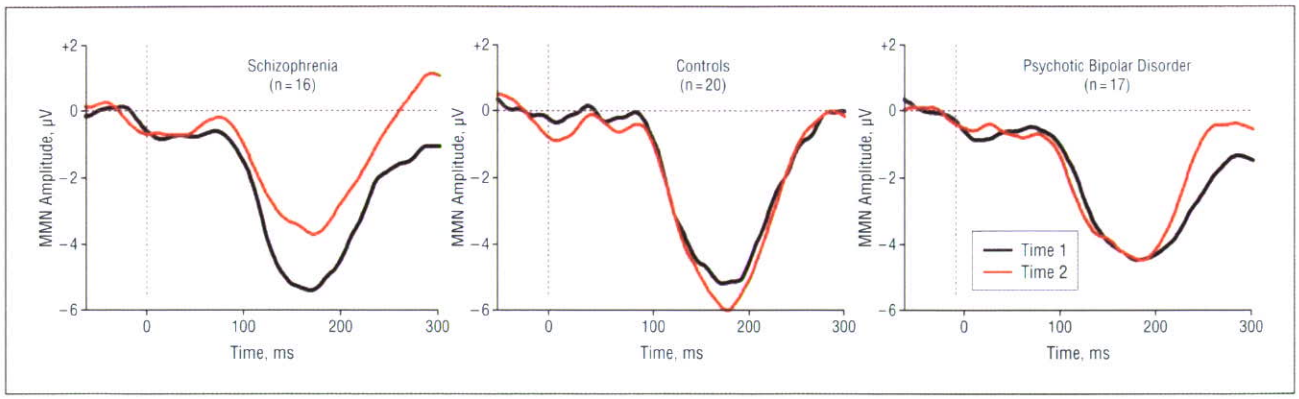


**Figure 3.** At longitudinal retesting, subjects with schizophrenia, who showed normal mean mismatch negativity (MMN) initially, now show significant reduction in MMN. Control subjects and subjects with bipolar disorder showed essentially no change in MMN amplitude.

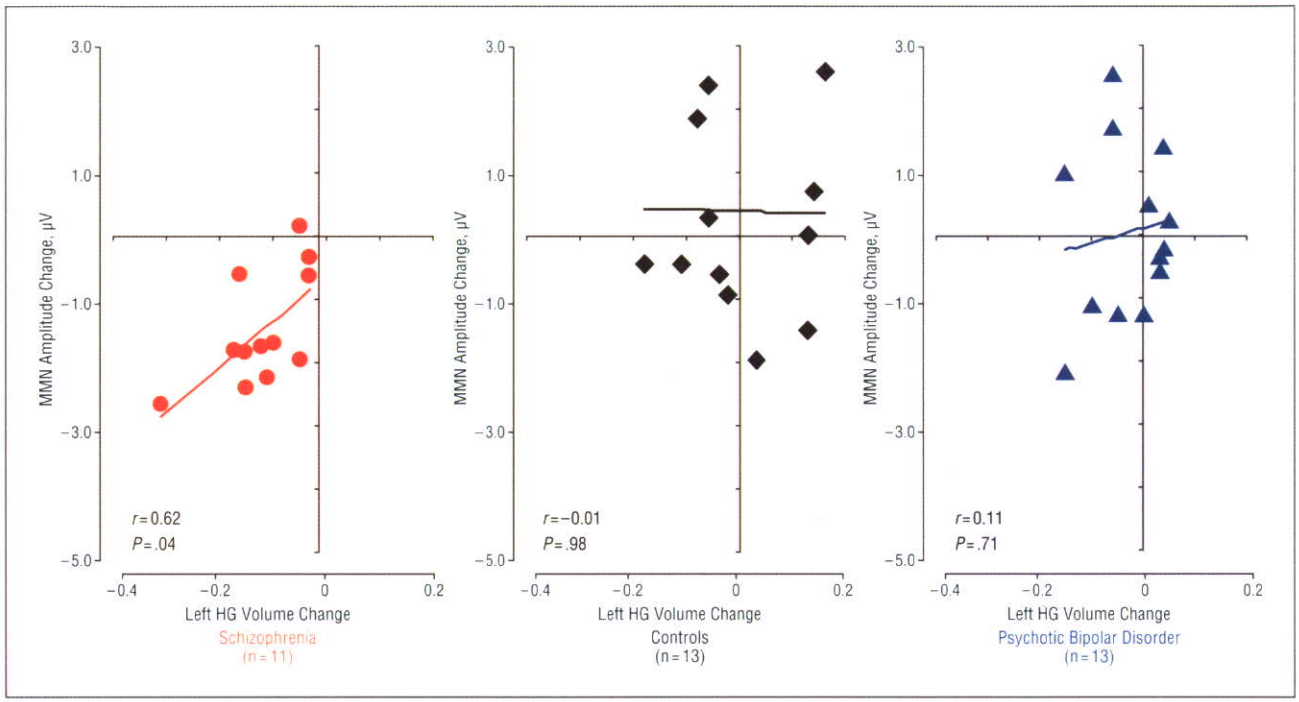


**Figure 4.** Relationship of mismatch negativity (MMN) amplitude reduction and left hemisphere primary auditory cortex gray matter volume loss. Whereas the subjects with bipolar disorder and control subjects cluster around 0 in both MMN amplitude change and gray matter change, those with schizophrenia are almost exclusively contained in the negative quadrant defined by MMN reduction and gray matter loss. HG indicates Heschl gyrus; colored lines, regression line.

Of primary importance was the tight interrelationship between the progressive reductions of MMN amplitude and left hemisphere Heschl gyrus gray matter volumes in schizophrenia. These reductions were highly correlated in subjects with schizophrenia ($r=0.62$; $P=.04$) but not in those with psychotic bipolar disorder or control subjects (**Figure 4**). In the schizophrenia group, the correlation between left hemisphere cortical gray matter change and MMN change was different from the correlation between right hemisphere change and MMN change (−0.12), attaining marginal significance ($P=.06$). Recall, however, that right Heschl gyrus volumes showed no significant change over time. The association between MMN decrement and left Heschl gyrus gray matter volume decrement in subjects with schizophrenia was significantly different from the association in the other groups ($P<.05$ for all). No significant associations with the left or right planum temporale were apparent. Furthermore, nearly all of the subjects with schizophrenia were in the quadrant defined by both MMN reduction and Heschl gyrus reduction. Assuming a chance distribution around the 2 dimensions, the expected random distribution would be 25% per quadrant. Neither control subjects nor those with bipolar disorder differed significantly from a random distribution ($\chi^2<1$ in each group; $P>.8$ for all). By contrast, subjects with schizophrenia were extremely different from a random distribution ($\chi^2=23.6$; $P<.001$).

## COMMENT

Several results support the presence of an active period of peri-onset cortical reduction in schizophrenia. At first hospitalization, only subjects with schizophrenia showed an abnormal brain volume–brain activity correlation be-

tween left hemisphere Heschl gyrus gray matter cortical volume and MMN amplitude, despite normal group mean amplitude and gray matter volume. This is consistent with a similar association between MMN and Heschl gyrus volume in chronic schizophrenia.[46] Subjects with psychotic bipolar disorder and control subjects likely had substantially more cortex than necessary to generate MMN and, hence, no statistical relationship between the size of their cortex and the size of their electrical response. The abnormal brain structure-function relationship at first hospitalization is consistent with progressive cortical reduction before the emergence of psychotic symptoms and cannot be explained by medication effects because most subjects were only acutely medicated after hospitalization. However, subjects with abnormally small MMN and Heschl gyrus volumes may well have had those abnormalities from birth, and only longitudinal testing can prove progressive reductions.

Longitudinal testing of MMN showed that nearly all subjects with schizophrenia showed MMN amplitude reduction and left hemisphere Heschl gyrus gray matter volume reduction. Of primary importance was a tight relationship between MMN reduction and gray matter loss. Highly related progressive abnormalities of functional and structural measures are present in schizophrenia after the first hospitalization. Therefore, MMN at initial hospitalization may serve as an index of the course of prehospitalization brain reduction in schizophrenia, and MMN subsequently may index continued cortical volume reduction.

Our ideas about the causes and course of schizophrenia need be readdressed. In the static lesion model of schizophrenia, which has been highly influential, prenatal or perinatal developmental abnormalities or insults form a primary static lesion with emergence of symptoms in young adulthood due to dysfunction of brain areas maturing later in life.[8] Alternative theories of combined early static and late progressive lesions have been proposed (eg, see Waddington et al[47] and Pantelis et al[48]), wherein the prenatal or perinatal neurodevelopmental abnormality interacts with some form of late-adolescent cortical gray matter reduction synergistically to cause psychosis. The MRI and MMN data from this study support the presence of a late progressive lesion.

The underlying biological mechanism of this late lesion is unknown. The schizophrenic brain as revealed through postmortem histologic examination is characterized by increased cell density,[49] smaller somal size,[50] reductions in the dendritic spines[51] in the tertiary frontal cortex, and smaller somal size[52] in the temporal cortices. These data indicate that schizophrenia is not characterized by classic neural degeneration but rather by a process of neuronal volume reduction that primarily involves dendrites.[53,54] Several candidate mechanisms for this reduction in dendrites have been suggested, including glutamatergic excitotoxicity[55-57] and synaptogenesis abnormalities.[56,58]

If glutamate plays a role in the late progressive lesion, there may be good reason why MMN seems to be a sensitive index of this process. Mismatch negativity reflects current inflow in *N*-methyl-D-aspartate glutamate receptors[59] and is reduced in healthy individuals after *N*-methyl-D-aspartate antagonists.[60] The relationship among MMN, *N*-methyl-D-aspartate glutamate receptors, and dendrite physiology may be especially important for understanding the brain abnormalities of schizophrenia. The association between MMN and progressive gray matter volume reduction has novel clinical implications; early pharmacologic intervention to prevent progressive cortical gray matter reduction may be tracked via the relatively noninvasive measurement of MMN amplitude.

Several caveats should be considered. Retest MRI may be confounded by changes in hydration and perfusion between images,[29] and medication may be associated with changes in cortical volumes, equivocally both increases[30] and reductions.[31,32] Subjects in this study were generally taking atypical medications, recently related to less cortical gray matter reduction.[31] Comparison of subjects with schizophrenia who were taking atypical medications at follow-up with those who were not revealed no significant differences in Heschl gyrus volume loss (effect size $d=0.23$) or MMN reduction (effect size $d=0.37$). Subjects who were taking atypical antipsychotics and those who were not showed cortical gray matter and MMN reduction, with relatively small effect sizes for increased loss if not medicated at all. In addition, testing of subjects with psychotic bipolar disorder who were receiving antipsychotic medications served as a natural control for medication effects, and those subjects showed no evidence of MMN or Heschl gyrus reductions. Furthermore, medication effects would be expected to be observed across the whole brain, yet the left, but not the right, Heschl gyrus was reduced in these subjects. These data weigh against any global hydration, perfusion, or medication effects. Second, subjects with schizophrenia lost to follow-up may differ significantly in terms of course from those who returned. There were moderately lower IQ and worse Global Assessment of Functioning scale scores in the lost subjects. However, both groups were relatively bright and significantly impaired. Third, other brain areas may show progressive reductions that correlate with MMN. We note that MMN generators are not distributed throughout the brain, and the temporal lobe accounts for much, if not all, MMN activity. Fourth, the single-rater intraclass correlations for Heschl gyrus volumes were high in all groups (subjects with schizophrenia, 0.96; subjects with bipolar disorder, 0.97; and control subjects, 0.93), but MMN reliabilities were lower (schizophrenic subjects, 0.74; bipolar subjects, 0.22; and control subjects, 0.52). We note that the schizophrenia group, where the main finding is present, was acceptably reliable. State effects might account for the low MMN reliability in subjects with bipolar disorder. Never rehospitalized subjects with bipolar disorder (n=11) showed an increase in MMN amplitudes (~27%), and those ever rehospitalized (n=9) showed a reduction (~20%). Finally, there were no associations between negative symptoms and MMN amplitudes at either time 1 or time 2, as has been reported in chronic schizophrenia.[61] Likewise, we did not detect any associations between MMN amplitudes and social functioning.[62] We suspect that the changing clinical picture of first-episode patients likely plays a role in this lack of associations. First-

hospitalized patients have not settled into a characteristic pattern or typical constellation of symptoms and present with extreme anxiety and turmoil in a state of symptom flux and evolution. Thus, the clinical and social functioning measures may have a relative emphasis on state rather than trait. We note that significant associations in the first-hospitalized schizophrenic subjects between anxiety at time 1 and subsequent MMN change ($r=-0.58$; $P=.06$) and Heschl change ($r=-0.77$; $P=.005$) highlight the unique clinical picture at protocol entrance. Furthermore, there was no association between anxiety at retest and MMN or Heschl gyrus change. At retesting a significant association between paranoia and MMN reductions emerged. Subjects with schizophrenia with the most paranoia at retest had the greatest MMN amplitude reductions ($r=-0.65$; $P=.03$), although the association with Heschl gyrus volume reduction did not attain significance ($r=-0.4$; $P=.25$).

In summary, these interrelated functional and structural measures support the presence of a late progressive lesion in schizophrenia. Mismatch negativity amplitude in schizophrenia, even when within the normal range, is tightly coupled to the volume of the underlying left temporal auditory cortex, shows progressive reductions coupled with ongoing cortical gray matter reduction of the left temporal auditory cortex, and, thus, may serve as a metric of successful interventions in halting such peri-onset progressive abnormalities.

**Submitted for Publication:** December 1, 2005; final revision received August 3, 2006; accepted August 12, 2006.
**Author Affiliations:** Veterans Affairs Boston Healthcare System, Brockton Division, Brockton (Drs Salisbury, Kuroki, Kasai, Shenton, and McCarley); Department of Psychiatry, Harvard Medical School, Boston (Drs Salisbury, Kuroki, Kasai, Shenton, and McCarley); Cognitive Neuroscience Laboratory, McLean Hospital, Belmont (Drs Salisbury, Shenton, and McCarley); and Surgical Planning Laboratory, Brigham and Women's Hospital, Boston (Drs Kuroki, Kasai, and Shenton), Mass. Drs Kuroki and Kasai are now with the Department of Neuropsychiatry, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.
**Correspondence:** Dean F. Salisbury, PhD, Department of Psychiatry, Harvard Medical School, 115 Mill St, Belmont, MA 02478 (dean_salisbury@hms.harvard.edu).
**Author Contributions:** Dr Salisbury had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
**Financial Disclosure:** None reported.
**Funding/Support:** This study was supported by Merit Awards (Drs McCarley and Shenton), Research Enhancement Award Program Awards (Drs McCarley and Shenton), and a Middleton Award (Dr McCarley) from the Department of Veterans Affairs; grants R01 MH 40799 and R01 MH 052807 (Dr McCarley), K05 MH 01110 and R01 MH 50747 (Dr Shenton), and R01 MH58704 (Dr Salisbury) from the National Institutes of Health; the MIND Foundation (Dr McCarley); and the National Alliance for Research on Schizophrenia and Depression (Dr Salisbury).
**Acknowledgment:** We thank Courtney Brown, BA, for help with data analysis.

## REFERENCES

1. Racenstein JM, Harrow M, Reed R, Martin E, Herbener E, Penn DL. The relationship between positive symptoms and instrumental work functioning in schizophrenia: a 10 year follow-up study. *Schizophr Res.* 2002;56:95-103.
2. Kraepelin E. *Psychiatrie: Ein Lehrbuch fur Studirende und Aerzte.* Leipzig, Germany: Verlag Von Johann Ambrosius Barth; 1899.
3. Bleuler E. *Dementia Praecox, or the Group of Schizophrenias.* Zinkin J, trans. New York, NY: International Universities Press; 1911.
4. O'Callaghan E, Sham P, Takei N, Glover G, Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet.* 1991;337:1248-1250.
5. Machón RA, Mednick SA, Schlusinger F. Seasonality, birth complications and schizophrenia in a high risk sample. *Br J Psychiatry.* 1987;151:122-124.
6. Weinberger DR, Wagner RL, Wyatt RJ. Neuropathological studies of schizophrenia: a selective review. *Schizophr Bull.* 1983;9:193-212.
7. Benes FM. Is there a neuroanatomical basis for schizophrenia? an old question revisited. *Neuroscientist.* 1995;1:104-115.
8. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry.* 1987;44:660-669.
9. O'Donnell BF, Faux SF, McCarley RW, Kimble MO, Salisbury DF, Nestor PG, Kikinis R, Jolesz FA, Shenton ME. Increased rate of P300 latency prolongation with age in schizophrenia: electrophysiological evidence for a neurodegenerative process. *Arch Gen Psychiatry.* 1995;52:544-549.
10. Davis KL, Buchsbaum MS, Shihabuddin L, Spiegel-Cohen J, Metzger M, Frecska E, Keefe RS, Powchik P. Ventricular enlargement in poor-outcome schizophrenia. *Biol Psychiatry.* 1998;43:783-793.
11. Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance study. *Arch Gen Psychiatry.* 2001;58:148-157.
12. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcomes: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry.* 2003;60:585-594.
13. Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, Bilder R. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry.* 2001;49:487-499.
14. DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res.* 1997;74:129-140.
15. DeLisi LE, Sakuma M, Maurizio AM, Relja M, Hoff AL. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. *Psychiatry Res.* 2004; 130:57-70.
16. Puri BK, Saeed N, Richardson AJ, Oatridge A, Hajnal JV, Bydder GM. Schizophrenia syndromes associated with changes in ventricle-to-brain ratios: a serial high-resolution three-dimensional magnetic resonance imaging study in first-episode schizophrenia patients using subvoxel registration and semiautomated quantification. *Int J Clin Pract.* 2005;59:399-402.
17. Cahn W, Hulshoff Pol HE, Lems EBTE, van Haren NEM, Schnack HG, van der Linden JA, Schothorst PF, van Engeland H, Kahn RS. Brain volume changes in first-episode schizophrenia: a 1 year follow-up study. *Arch Gen Psychiatry.* 2002; 59:1002-1010.
18. Wood SJ, Velakoulis D, Smith DJ, Bond D, Stuart GW, McGorry PD, Brewer WJ, Bridle N, Eritaia J, Desmond P, Singh B, Coplov D, Pantelis C. A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. *Schizophr Res.* 2001;52:37-46.
19. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC. A follow-up magnetic resonance imaging study of schizophrenia: relationship of neuroanatomical changes to clinical and neurobehavioral outcomes. *Arch Gen Psychiatry.* 1998;55:145-152.
20. Bachmann S, Bottmer S, Pantel J, Schröder J, Amann M, Essig M, Schad LR. MRI-morphometric changes in first-episode schizophrenia patients at 14 months follow-up. *Schizophr Res.* 2004;67:301-303.
21. Rapoport JL, Geidd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A. Progressive cortical change during adolescence in childhood onset schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry.* 1999;56: 649-654.
22. Thompson PM, Vidal C, Geidd JN, Gochman P, Blumenthal J, Nicolson R, Toga AW, Rapoport JL. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc Natl Acad Sci U S A.* 2001;98:11650-11655.
23. Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Lee CU, Ciszewski AA, Yurgelun-Todd DA, Kikinis R, Jolesz FA, McCarley RW. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. *Am J Psychiatry.* 2003;160:156-164.

24. Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Spencer M, Yurgelun-Todd DA, Kikinis R, Jolesz FA, McCarley RW. Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry.* 2003; 60:766-775.
25. Shenton ME, Dickey C, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res.* 2001;49:1-52.
26. Cannon TD, Thompson PM, van Erp TGM, Toga AW, Poutanen VP, Huttunen M, Lonnqvist J, Standerskjold-Nordenstam CG, Narr KL, Khaledy M, Zoumalan CI, Dail R, Kaprio J. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. *Proc Natl Acad Sci U S A.* 2002;99:3228-3233.
27. Molina V, Sanz J, Sarramea F, Benito C, Palomo T. Lower prefrontal gray matter volume in schizophrenia in chronic but not in first episode schizophrenia patients. *Psychiatry Res.* 2004;131:45-56.
28. Sporn AL, Greenstein DK, Gogtay N, Jeffries NO, Lenane M, Gochman P, Clasen LS, Blumenthal J, Geidd JN, Rapoport JL. Progressive brain volume loss during adolescence in childhood onset schizophrenia. *Am J Psychiatry.* 2003;160:2181-2189.
29. Weinberger DR, McClure RK. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenia brain? *Arch Gen Psychiatry.* 2002;59:553-558.
30. Keshavan MS, Haas GL, Kahn CE, Aguilar E, Dick EL, Schooler NR, Sweeney JA, Pettigrew JW. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *J Psychiatr Res.* 1998;32:161-167.
31. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RSE, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry.* 2005;62:361-370.
32. Dazzan P, Morgan KD, Orr K, Hutchinson G, Chitnis X, Suckling J, Fearon P, McGuire PK, Mallett RM, Jones PB, Leff J, Murray RM. Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. *Neuropsychopharmacology.* 2005;30:765-774.
33. Näätänen R. The role of attention in auditory information processing as revealed by event-related potentials and other measures of cognitive function. *Behav Brain Sci.* 1990;13:201-288.
34. Hari R, Hamalainen M, Ilmoniemi R, Kaukoranta E, Reinikainen K, Salminen J, Alho K, Näätänen R, Sams M. Responses of the primary auditory cortex to pitch changes in a sequence of tone pips: neuromagnetic recordings in man. *Neurosci Lett.* 1984;50:127-132.
35. Javitt DC, Steinschneider M, Schroeder CE, Vaughan HG Jr, Arezzo JC. Detection of stimulus deviance within primate primary auditory cortex: intracortical mechanisms of mismatch negativity (MMN) generation. *Brain Res.* 1994;667:192-200.
36. Kropotov JD, Näätänen R, Sevostianov AV, Alho K, Reinikainen K, Kropotova OV. Mismatch negativity to auditory stimulus change recorded directly from the human temporal cortex. *Psychophysiology.* 1995;32:418-422.
37. Javitt DC, Doneshka P, Grochowski S, Ritter W. Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Arch Gen Psychiatry.* 1995;52:550-558.
38. Catts SV, Shelley AM, Ward PB, Liebert B, McConaghy N, Andrews S, Michie PT. Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *Am J Psychiatry.* 1995;152:213-219.
39. Salisbury DF, Shenton ME, Griggs CB, Bonner-Jackson A, McCarley RW. Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. *Arch Gen Psychiatry.* 2002;59:686-694.
40. Morosan P, Rademacher J, Schleicher A, Amunts K, Schormann T, Ziles K. Human primary auditory cortex: cytoarchitectonic subdivisions and mapping into a spatial reference system. *Neuroimage.* 2001;13:684-701.
41. Sweet RA, Dorph-Petersen KA, Gundersen HJ, Lewis DA. Location and volumes of the auditory core, lateral belt, and parabelt cortices in the human superior temporal gyrus [abstract]. *Schizophr Bull.* 2005;31:262.
42. Hollingshead AB. *Two-Factor Index of Social Position.* New Haven, Conn: Yale Station; 1965.
43. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia.* 1971;9:97-113.
44. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale–Revised.* Cleveland, Ohio: Psychological Corp; 1981.
45. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962; 10:799-812.
46. Ward PB, Loneragan C, Liebert B, Catts SV, Chaturvedi S, Pearson M, Ganser EL, Redenbach J, Michie PT, Andrews S, McConaghy N. MRI measures of auditory cortex area correlate with an ERP index of auditory sensory memory in schizophrenia [abstract]. *Schizophr Res.* 1995;15:102.
47. Waddington JL, Scully PJ, Youssef HA. Developmental trajectory and disease progression in schizophrenia: the conundrum, and insights for a 12 year prospective study in the Monaghan 101. *Schizophr Res.* 1997;23:107-118.
48. Pantelis C, Yücel M, Wood SJ, McGorry PD, Velakoulis D. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. *Aust N Z J Psychiatry.* 2003;37:399-406.
49. Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry.* 1999;45:17-25.
50. Pierri JN, Volk CE, Auh S, Sampson A, Lewis DA. Decreased somal size of deep layer 3 pyramidal neurons in the prefrontal cortex of subjects with schizophrenia. *Arch Gen Psychiatry.* 2001;58:466-473.
51. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry.* 2000;57:65-73.
52. Sweet RA, Pierri JN, Auh S, Sampson A, Lewis DA. Reduced pyramidal cell somal volume in auditory association cortex of subjects with schizophrenia. *Neuropsychopharmacology.* 2003;28:599-609.
53. McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch Gen Psychiatry.* 2000;57:637-648.
54. Feinberg I. Schizophrenia: caused by a fault during programmed synaptic elimination during adolescence? *J Psychiatr Res.* 1983;17:319-334.
55. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry.* 1995;52:998-1007.
56. Coyle JT. The glutamate dysfunction hypothesis for schizophrenia. *Harv Rev Psychiatry.* 1996;3:241-253.
57. McCarley RW, Hsiao JK, Freedman R, Pfefferbaum A, Donchin E. Neuroimaging and the cognitive neuroscience of schizophrenia. *Schizophr Bull.* 1996;22: 703-725.
58. Konradi C, Heckers S. Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. *Pharmacol Ther.* 2003;97:153-179.
59. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical *N*-methyl D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc Natl Acad Sci U S A.* 1996;93: 11962-11967.
60. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt D. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers. *Arch Gen Psychiatry.* 2000;57:1139-1147.
61. Javitt DC, Shelly AM, Ritter W. Associated deficits in mismatch negativity generation and tone matching in schizophrenia. *Clin Neurophysiol.* 2000;111:1733-1737.
62. Light GA, Braff D. Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. *Arch Gen Psychiatry.* 2005;62:127-136.

Available online at www.sciencedirect.com
ScienceDirect
Schizophrenia Research 99 (2008) 250–262
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

# Reduced frontopolar activation during verbal fluency task in schizophrenia: A multi-channel near-infrared spectroscopy study

Ryu Takizawa [a,*], Kiyoto Kasai [a], Yuki Kawakubo [a], Kohei Marumo [a], Shingo Kawasaki [b], Hidenori Yamasue [a], Masato Fukuda [c]

[a] *Department of Neuropsychiatry, Graduate school of Medicine, The University of Tokyo, Tokyo, Japan*
[b] *Hitachi Medical Corporation, Application Development Office, Optical Topography Group, Tokyo, Japan*
[c] *Department of Psychiatry and Human Behavior, Graduate School of Medicine, Gunma University, Maebashi, Japan*

Received 17 June 2007; received in revised form 20 September 2007; accepted 18 October 2007
Available online 11 December 2007

**Abstract**

Functional neuroimaging studies to date have shown prefrontal dysfunction during executive tasks in schizophrenia. However, relationships between hemodynamic response in prefrontal sub-regions and clinical characteristics have been unclear. The objective of this study is to evaluate prefrontal hemodynamic response related to an executive task in schizophrenia and to assess the relationship between activation in the prefrontal sub-regions and clinical status. Fifty-five subjects with schizophrenia and age- and gender-matched 70 healthy subjects were recruited for this case-control study in a medical school affiliated hospital in the Tokyo metropolitan area, Japan. We measured hemoglobin concentration changes in the prefrontal (dorsolateral, ventrolateral, and frontopolar regions) and superior temporal cortical surface area during verbal fluency test using 52-channel near-infrared spectroscopy, which enables real-time monitoring of cerebral blood volumes in the cortical surface area under a more restraint-free environment than positron emission tomography or functional magnetic resonance imaging. The two groups showed distinct spatiotemporal pattern of oxy-hemoglobin concentration change during verbal fluency test. Schizophrenia patients were associated with slower and reduced increase in prefrontal activation than healthy controls. In particular, reduced activations of the frontopolar region, rather than lateral prefrontal or superior temporal regions, showed significant positive correlations with lower global assessment of functioning scores in the patient group, although task performance was not significantly associated with the scores. These results suggest that reduced frontopolar cortical activation is associated with functional impairment in patients with schizophrenia and that near-infrared spectroscopy may be an efficient clinical tool for monitoring these characteristics.


*Keywords:* Schizophrenia; Near-infrared spectroscopy (NIRS); Frontopolar prefrontal cortex; Verbal fluency test; Global assessment of functioning (GAF)

## 1. Introduction

Neuroimaging studies have identified schizophrenia as being associated with dysfunction of the prefrontal cortex (Callicot et al., 2000; Carter et al., 1998; Curtis et al., 1998), an area involved in almost all high-level cognitive functions such as working memory, memory

* Corresponding author. Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel.: +81 3 5800 9263; fax: +81 3 5800 6894.
*E-mail address:* takizawar-tky@umin.ac.jp (R. Takizawa).

0920-9964/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2007.10.025

retrieval, executive function, and language (Cabeza and Nyberg, 2000). Moreover, recent advances in neuroscience have sought to clarify functional segregation in the prefrontal cortical surface areas such as dorsolateral, ventrolateral, and frontopolar (anterior frontal) regions (Daw et al., 2006; Fletcher and Henson, 2001; Fox et al., 2006). The ventrolateral and dorsolateral sub-regions are involved in the updating/maintenance of information and to the selection/manipulation/monitoring of that information, respectively (Fletcher and Henson, 2001). In contrast, frontopolar cortex (BA 10), which has been suggested to have enlarged and become specialized during hominid evolution (Semendeferi et al., 2001), provides higher level of control to coordinate ventrolateral and dorsolateral functions in order to maximize task performance (Koechlin et al., 1999; Fletcher and Henson, 2001; Braver and Bongiolatti, 2002), which has led to the idea that frontopolar region is likely to have a vital role in achieving high-order executive control in everyday life (Burgess et al., 2000). However, it remains unclear which specific sub-regions of the prefrontal cortex is most directly associated with clinical characteristics in schizophrenia.

An independent line of work has suggested that cognitive deficits as indexed by neuropsychological assessments are more tightly coupled with social functioning in patients with schizophrenia than positive or negative symptoms (Green, 1996; Green et al., 2000; Green et al., 2004; Flashman and Green, 2004). Whereas progress has been made for an association between psychosocial impairment and electrophysiological measures such as P300, N200b, and mismatch negativity event-related potentials (Ikebuchi et al., 1996; Iwanami et al., 1999; Kawakubo and Kasai, 2006; Light and Braff, 2005; Ohno et al., 2000) and brain morphological measures (Ho et al., 2003; Milev et al., 2003; Prasad et al., 2005; Staal et al., 2001; Wassink et al., 1999), the relationships between functional hemodynamic response in the sub-regions of the prefrontal cortex and clinical characteristics in schizophrenia has been unclear. These research questions may be an important step towards developing an objective monitoring tool and ultimately an effective intervention strategy for cognitive and social dysfunction in schizophrenia.

Multi-channel near-infrared spectroscopy (NIRS), a recently developed functional neuroimaging technology, enables the non-invasive detection of spatiotemporal characteristics of brain function (Strangman et al., 2002a, 2003; Boas et al., 2004; Huppert et al., 2006). NIRS has enabled non-invasive and bedside measurement of the concentrations of oxy-hemoglobin ([oxy-Hb]) and deoxy-hemoglobin ([deoxy-Hb]), which are assumed to reflect the regional cerebral blood volume (rCBV). While functional brain imaging methodologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have an excellent spatial resolution, they are limited in that they require large apparatuses which prevents their use in a bedside setting for diagnostic and treatment purposes. In contrast, NIRS is a neuroimaging modality that, for the following reasons is especially suitable for psychiatric patients (Matsuo et al., 2003a). First, because NIRS is relatively insensitive to motion artifact, it can be applied to experiments that might cause some motion of the subjects such as vocalization. Second, the subject can be examined in a natural sitting position, without any surrounding distraction. Third, the cost is much lower than other neuroimaging modalities and the set-up is very easy. Fourth, the high temporal resolution of NIRS is useful in characterizing the time course of prefrontal activity of psychiatric disorders (Kameyama et al., 2006; Suto et al., 2004). Accordingly, NIRS has been used to assess brain functions in many psychiatric disorders, including schizophrenia, bipolar disorder, depression, dementia, post traumatic stress disorder, and pervasive developmental disorders (Fallgatter et al., 1997; Hock et al., 1997; Kameyama et al., 2006; Kubota et al., 2005; Kuwabara et al., 2006; Matsuo et al., 2003a, b, 2004; Shinba et al., 2004; Suto et al., 2004).

A previous study (Suto et al., 2004) showed reduced [oxy-Hb] changes in the prefrontal cortex during verbal fluency task in patients with schizophrenia using a NIRS machine with insufficient coverage of important sub-regions of the prefrontal cortex such as ventrolateral portions. The purpose of the present study was to use an NIRS machine with a wide coverage of the prefrontal cortex in order to investigate more precisely the relationship between activity in the prefrontal sub-regions and the clinical characteristics in a larger group of patients with schizophrenia.

## 2. Materials and methods

### 2.1. Subjects

Fifty-five patients with schizophrenia and 70 age- and gender-matched healthy subjects participated in the study (Table 1). All the participants were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native Japanese speakers.

The patients were recruited among outpatients and inpatients at the University of Tokyo Hospital. Diagnosis of schizophrenia was made through the Structured Clinical Interview for DSM-IV Axis I Disorders (First

Table 1
Clinical characteristics of the study groups

| | Patients with schizophrenia ($N$=55) | | Healthy subjects ($N$=70) | | Group difference $P$ value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age, year | 40.1 | 11.1 | 37.4 | 13.6 | .22 |
| Gender, women/men | 26/29 | | 34/36 | | .89[a] |
| Handedness | 92.4 | 17.3 | 92.9 | 16.3 | .85 |
| Education, year | 14.7 | 2.5 | 15.6 | 2.0 | .022 |
| Self socio-economic status (SES) | 3.4 | 1.1 | 2.0 | .6 | <.001 |
| Parental SES | 2.5 | .7 | 2.3 | .7 | .18 |
| Estimated premorbid IQ | 102.3 | 12.2 | 108.3 | 9.8 | .006 |
| Number of words generated | 14.3 | 4.6 | 17.3 | 4.4 | <.001 |
| Age at onset, years | 26.4 | 8.7 | NA | | |
| Duration of illness, years | 13.8 | 10 | NA | | |
| PANSS | | | | | |
| Positive | 16.7 | 5.6 | NA | | |
| Negative | 21.6 | 6.4 | NA | | |
| General psychopathology | 38.2 | 7.9 | NA | | |
| Global Assessment of Functioning (GAF) | 47.2 | 12.9 | NA | | |
| Medication | | | | | |
| Chlorpromazine equivalent dose, mg/day | 778 | 655 | NA | | |
| Diazepam equivalent dose, mg/day | 13.4 | 18.5 | NA | | |
| Biperiden equivalent dose, mg/day | 3.2 | 2.3 | NA | | |

Abbreviations: IQ, Intelligence Quotient; PANSS, Positive and Negative Symptom Scale; NA, not applicable.
[a] Chi-square test was used for testing group difference. Otherwise, $t$-test was used.

et al., 1997) by an experienced psychiatrist (K.K.). For screening of healthy subjects, SCID non-patient edition (SCID-NP) was used. On the same day as the near-infrared spectroscopy (NIRS) experiment, psychiatric symptoms and the level of social functioning were evaluated by one psychiatrist (K.K.) using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Global Assessment of Functioning scores (GAF) (American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data. At the time of the study, the patients with schizophrenia were on medication with antipsychotics and/or anxiolytics and/or antiparkinsonian agents. Socioeconomic status (SES) and parental SES were assessed using the Hollingshead scale (Hollingshead, 1965). Premorbid IQs were estimated using Japanese version of the National Adult Reading Test (Matsuoka et al., 2006) (Table 1). The reliability of the GAF as an assessment of social functioning was confirmed based on the high correlation between GAF scores and total scores on the Japanese version of Life Skills Profile ($N$=55, $r$=.61, $P$<.001) (Parker et al., 1991; Japanese version, Hasegawa et al., 1997).

The exclusion criteria for both groups were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and alcohol/substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease in themselves or a family history of axis I disorder in their first-degree relatives. The ethical committee of the Hospital of Tokyo University approved this study. All subjects gave written informed consent according to the Declaration of Helsinki after a complete explanation of the study.

### 2.2. Activation task

[Hb] changes were measured during a cognitive activation task. Each participant sat on a comfortable chair with their eyes open throughout the measurements. The subjects were instructed to minimize movement such as head movements, strong biting and eye blinking during the NIRS measurements, for they can produce artifacts or changes in cerebral perfusion unrelated to the task.

The cognitive activation task included a 30-s pre-task baseline, a 60-s verbal fluency task (letter version), and a 70-s post-task baseline. The verbal fluency test was chosen, because it has been often used for cognitive activation in NIRS studies, and previous reports showed measurable prefrontal activation during the letter fluency task in healthy subjects (Herrmann et al., 2003, 2006; Kameyama et al., 2004). This procedure was similar to that of Suto et al. (2004), Ito et al. (2005) and Kameyama

et al. (2006) except for the use of a 70-s post-task baseline instead of their 60 s, to enable a more complete return of [Hb] change to the baseline in the post-task period.

For the pre- and post-task baseline periods, the subjects were instructed to repeat Japanese vowels (/a/, /i/, /u/, /e/ and /o/) aloud. This was intended to correct the data during the fluency task for activation due to vocalization.

During the verbal fluency task period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible, which is commonly used in Japanese letter version of the verbal fluency task since Japanese words inevitably begin with a vowel or consonant-vowel syllable. The three initial syllables (first; /to/, /a/, or /na/, second; /i/, /ki/, or /se/, third; /ta/, /o/, or /ha/) were presented in the order which was counterbalanced among the subjects and changed every 20 s during the 60-second task to reduce the time during which the subjects remained silent. The subjects were instructed by an auditory cue at the start and end of the task and when the syllable was changed. Because the number of words generated was not significantly different among the three initial syllables (one-way repeated measures ANOVA; $F[2, 123]=1.28$, $P=.28$, n.s.), the total of correct words generated during verbal fluency tasks was defined as a measure of task performance (Table 1).

### 2.3. NIRS measurement

The 52-multi-channel NIRS machine (ETG-4000, Hitachi Medical Co.) measures relative changes of [oxy-Hb] and [deoxy-Hb] using two wavelengths (695 nm and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). The [total-Hb] was calculated as the sum of [oxy-Hb] and [deoxy-Hb]. In this system, these [Hb] values include differential pathlength factor (DPF). The distance between pairs of source-detector probes was set at 3.0 cm and we defined each measuring area between pairs of source-

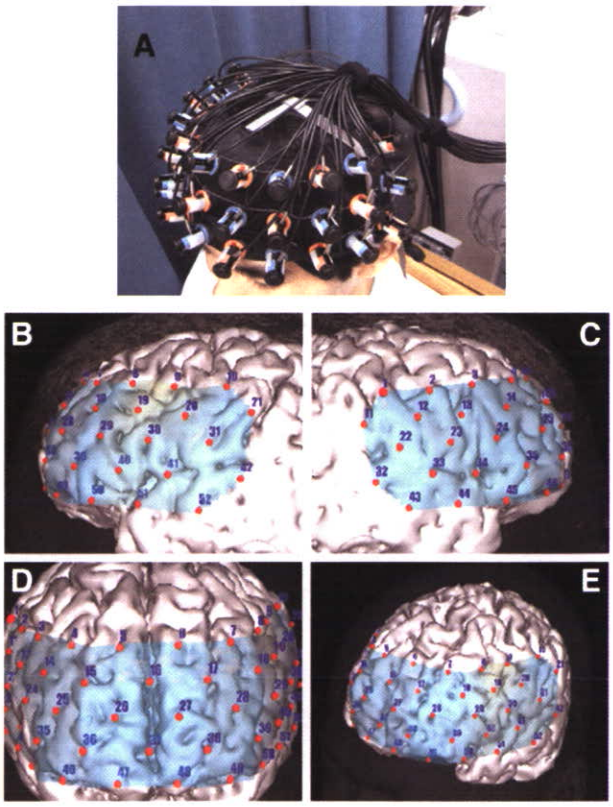


Fig. 1. The probe setting and measurement points of 52-channel near-infrared spectroscopy (NIRS). Panel A: the probes with thermoplastic 3 × 11 shells were placed over a subject's bilateral frontal regions. Panels B–E: the 52 measuring positions of the NIRS machine are superimposed on 3D-reconstructed cerebral cortical surface from magnetic resonance imaging of a representative subject. The channel numbers are indicated above the measuring points.