study has demonstrated that childhood sexual or physical abuse is associated with an increased plasma ACTH concentration and enhanced cortisol responses to DEX/CRH [Heim et al., 2008]. Carpenter et al. [2009] revealed using CTQ that childhood emotional abuse is associated with the dampening of cortisol response to DEX/CRH. On the basis of this finding together with the above-mentioned previous findings, they proposed that different types of parenting experience during childhood and adolescence (emotional, physical, or sexual abuse) might portend different consequences with regard to HPA axis activity in adulthood, that is, childhood emotional or physical abuse is likely associated with HPA axis hypoactivity in adulthood, whereas childhood sexual abuse is likely associated with HPA axis hyperactivity in adulthood. CTQ is one of the widely used self-report measurements to examine the association of neuroendocrine challenge test with parenting experiences during childhood and adolescence. Although it is expected that both CTQ and PBI should have been scored and analyzed in this study, we were unable to administer CTQ unfortunately, because the Japanese version of which has not yet been developed. Different from studies using neuroendocrine challenge tests, Engert et al. [2010b] described that in young adults without psychiatric disorders, the maternal medium-care-score group shows a greater cortisol response to a psychosocial task [i.e., TSST; a 10-min free speech in front of panelists and a camera] [Kirschbaum et al., 1993], compared with the maternal low- and high-care-score groups. However, we failed to find significant associations in all comparisons of AUC_{net} cortisol among the parental low-, medium- and high-care-score groups in this study. As the reasons for this discrepancy between the findings of the two studies, the following are proposed. Because in this study we focused on the associations of HPA axis hypoactivity with PBI score and hippocampal GM volume, we excluded 8 of the 48 subjects who possibly showed HPA axis hyperactivity, as determined by the DEX test, which measures the negative feedback effects of DEX via anterior pituitary glucocorticoid receptor activation [Pariante and Miller, 2001]. On the other hand, the study by Engert et al. [2010b] may have included subjects with HPA axis hyperactivity as study samples, because their subjects were not subjected neuroendocrine challenge tests such as the DEX test; thus, data of those subjects might have affected their findings. Second, the DEX/CRH test contains the suppressive effect of DEX on the pituitary-adrenal response to CRH and the facilitative effect of CRH on ACTH and cortisol release [Kunugi et al., 2006], whereas a cortisol response to TSST could reflect an ability to cope with psychosocial stress in each individual, because TSST combines uncontrollable and socioevaluative elements [Dickerson and Kemeny, 2004]. On the basis of above-mentioned characteristic features of TSST, Engert et al. [2010b] described that in their study, the medium-care-score group likely has the adaptive coping ability and an average cortisol response to psychosocial stress, but the low- and high-care-score groups may tend to show HPA axis hypoactivity, resulting in the maternal medium-care-score group, showing a significantly excessive cortisol response to TSST than the maternal low- and high-care-score groups. Finally, as a major cause, the effect of statistical type II error on our results in this study must be considered. In this study, rank correlation analyses and comparison between two groups (i.e., low- and high-PBI-score groups) showed significant associations between AUC_{net} cortisol and parental overprotection scores of PBI, but no significant association was found in all comparisons of AUC_{net} cortisol among low-, medium- and high-PBI-score groups, suggesting that type II error could affect the results of comparison among the three groups, owing to the small number of our subjects. Thus, further analysis with a larger number of subjects is required.

As a possible explanation of how chronic stress during childhood and adolescence induces adulthood cortisol hyporeactivity in response to DEX/CRH, it is hypothesized on the basis of a developmental model that a trajectory of initial hyperactivation of the HPA system could progress to a state of chronic adrenal stress hypoactivity [Fries et al., 2005; Pryce et al., 2005] as a type of counter-regulatory adaptation after acute or sustained exposure to excessive ACTH levels during a stressful early developmental period [Miller et al., 2007]. As several previous animal studies reported CRH hypersecretion from the hypothalamus and adaptive down-regulation of CRH receptors under continuous stress [Hauger et al., 1988; Makino et al., 1994], CRH receptor downregulation might be involved in reduced ACTH levels and an attenuated cortisol response to CRH. In addition, reduced biosynthesis or depletion at several levels of the HPA axis (CRH, ACTH, and/or cortisol) after enhanced secretions of these hormones under continuous stress might contribute to cortisol hyporeactivity in response to DEX/CRH [Heim et al., 2000]. Furthermore, an increased sensitivity to the HPA axis for a negative feedback is suggested to attenuate the cortisol response [Yehuda et al., 1991].

A significant positive association was found between HPA axis hypoactivity and hippocampal GM volume reduction in healthy young adults in this study. The mechanisms by which chronic HPA axis hypoactivity contributes to the GM volume reduction of the hippocampus are explained as follows. Because *myo*-inositol level is considered to be an astrocyte marker and *myo*-inositol induces cell membrane metabolism and osmoregulation, removal of cortisol is reported to induce the decrease in *myo*-inositol level in the hippocampus [Brand et al., 1993; Heilig et al., 1989; Schubert et al. 2008]. Thus, it is suggested that HPA axis hypoactivity induces an altered astrocyte metabolism or an electrolyte disturbance such as hyponatremia, leading to hippocampal neurodegeneration and insufficient GM development in the hippocampus with time [Fries et al., 2005].

The results of our study seem to support the hypothesis that parenting overprotection during childhood and

adolescence could induce the reduction of hippocampal GM volume in adulthood via HPA axis hypoactivity. However, we failed to show the direct association of PBI scores with total or regional hippocampal GM volume. Some previous research showed a significant association between childhood maltreatment and reduction of hippocampal GM volume in adulthood [Bremner et al., 2003; Stein et al., 1997; Woon and Hedges, 2008]. These studies have included patients with current PTSD related to maltreatment as study subjects, which differed from our study. Thus, the above-mentioned statistical insignificance in this study might result from our sampling method, i.e., only adults without a history of childhood traumatic events and current psychiatric disorders including PTSD were enrolled. As another possibility, statistical type II error might be the cause of this absence of significant association, owing to the small sample size of this study. Indeed, Pearson's simple correlation showed a significant negative relationship between parental overprotection score and total hippocampal GM volume in this study, but this significance did not remain after adjustments for age, gender, and total GM volume.

Another study by Engert et al. [2010a] revealed in the elderly adults without psychiatric disorders a significant positive association between hippocampal GM volume and parental care score of PBI, as well as a significant negative association between hippocampal GM volume and cortisol response to psychosocial stress task (MIST; subjects perform an arithmetic task and receive a negative feedback to its performance) [Dedovic et al., 2005]. On the basis of these findings, they suggested a notable neurodevelopmental model, i.e., parental low-care during childhood and adolescence induces an adulthood HPA axis hyperactivity via hippocampal GM volume reduction. On the other hand, our finding in this study showed no significant association between PBI scores and hippocampal GM volume reduction. Different from our subjects in this research, the study by Engert et al. [2010a,b] did not exclude subjects with a possible HPA axis hyperactivity. As a result, the associations of HPA axis hyperactivity with hippocampal GM volume and PBI score might mask the statistically significant associations of HPA axis hypoactivity with them. Furthermore, the age difference between the subjects in the study by Engert et al. [2010a] and those in our study (i.e., elderly or young adults) should be considered because a number of studies of humans and experimental animals provide evidence that HPA axis hyperactivity contributes to degeneration of neurons, including those in the hippocampus, associated with aging [Ferrari et al., 1995; Lupien et al., 1998; Sapolsky, 1999, Swaab et al., 2005].

In this study, we used 0.5 mg of DEX in the DEX/CRH test because a higher sensitivity of the 0.5 mg DEX test has been reported in the Japanese/Asian populations [Matsunaga and Sarai, 2000]. However, there is no evidence that the DEX (0.5 mg)/CRH test is recommended for any populations on the basis of their DEX/CRH sensitivity. In most of the previous studies using the DEX/CRH test, researchers used 1–1.5 mg of DEX to determine HPA axis hyperactivity in patients with several psychiatric disorders, such as major depression [Kunugi et al., 2006], whereas the DEX test at a low dose of DEX (0.5 mg) has been frequently performed to estimate HPA axis hypoactivity in patients with PTSD [Yehuda et al., 1993]. Accordingly, further research using the DEX/CRH test at conventional doses of DEX (1–1.5 mg) will be required to examine associations among parenting experiences during childhood and adolescence, HPA axis hypoactivity, and hippocampal GM volume.

In addition to sample size, subject selection, and the dose of DEX in the DEX/CRH test there were some limitations in this study as follows. PBI is an instrument for measuring retrospectively recalled parental behaviors, which leaves it open to possible influences of current mood state or recall bias. Moreover, we were unable to obtain a causal relationship among parenting overprotection during childhood and adolescence, HPA axis hypoactivity, and hippocampal GM volume reduction, because of the cross-sectional study design and the lack of subjects in other age ranges, i.e., childhood and adolescence. In addition, other lines of evidence showed that variation of the corticotropin-releasing hormone receptor (CRHR1) gene could moderate the effect of childhood maltreatment on cortisol response to DEX/CRH in adulthood [Tyrka et al., 2009]. Thus, further research with a larger sample size, including patients with past and current PTSD, using other doses of DEX in the DEX/CRH test, and taking heredity into consideration (i.e., CRHR1 gene types) will be required.

In conclusion, statistically significant associations were found between parental overprotection during childhood and adolescence and adulthood HPA axis hypoactivity, and between HPA axis hypoactivity and hippocampal GM volume reduction in healthy young adults, but no significant relationship was observed between any PBI scores and adulthood hippocampal GM volume. The findings of this study will increase our understanding of associations among parenting experiences during childhood and adolescence, HPA axis activity, and hippocampal GM development.

ACKNOWLEDGMENTS

All the authors declare that they have no actual or potential conflicts of interest. They are deeply grateful to all the subjects as well as all the medical staff members involved in this project. The funding agency played no role in the study design, collection, analysis or interpretation of data, writing of the report, or decision to submit the paper for publication.

REFERENCES

Aihara M, Ida I, Yuuki N, Oshima A, Kumano H, Takahashi K, Fukuda M, Oriuchi N, Endo K, Matsuda H, Mikuni M (2007):

HPA axis dysfunction in unmedicated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions. Psychiatry Res 155:245–256.

Ashburner J, Friston K (2000): Voxel-based morphometry—The methods. Neuroimage 11:805–821.

Brand A, Richter-Landsberg C, Leibfritz D (1993): Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. Dev Neurosci 15:289–298.

Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, Vaccarino LV, Soufer R, Garg PK, Ng CK, Staib LH, Duncan JS, Charney DS (2003): MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry 160:924–932.

Brett M, Anton J, Valabregue R, Poline J (2002): Region of interest analysis using an SPM toolbox [abstract]. Paper presented at the Eighth International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Carpenter LL, Tyrka AR, Ross NS, Khoury L, Anderson GM, Price LH (2009): Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. Biol Psychiatry 66:69–75.

Claes SJ (2004): Corticotropin-releasing hormone (CRH) in psychiatry: From stress to psychopathology. Ann Med 36:50–61.

Conrad CD (2008): Chronic stress-induced hippocampal vulnerability: The glucocorticoid vulnerability hypothesis. Rev Neurosci 19:395–411.

Dedovic K, Renwick R, Mahani NK, Engert V, Lupien SJ, Pruessner JC (2005): The Montreal imaging stress task: Using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. J Psychiatry Neurosci 30:319–325.

Dickerson SS, Kemeny ME (2004): Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. Psychol Bull 130:355–391.

Engert V, Buss C, Khalili-Mahani N, Wadiwalla M, Dedovic K, Pruessner JC (2010a) Investigating the association between early life parental care and stress responsivity in adulthood. Dev Neuropsychol 35:570–581.

Engert V, Efanov SI, Dedovic K, Duchesne A, Dagher A, Pruessner JC (2010b) Perceived early-life maternal care and the cortisol response to repeated psychosocial stress. J Psychiatry Neurosci 35:370–377.

Ferrari E, Magri F, Dori D, Migliorati G, Nescis T, Molla G, Fioravanti M, Solerte SB (1995): Neuroendocrine correlates of the aging brain in humans. Neuroendocrinology 61:464–470.

First MB, Spitzer RL, Gibbon M, Williams JBW (1996): Structured Clinical Interview for DSM-IV Axis I Disorders, Version 2.0. New York: New York State Psychiatric Institute.

First MB, Spitzer RL, Williams JBW, Gibbon M (1997): Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) User's Guide and Interview. Washington DC: American Psychiatric Press.

Fries E, Hesse J, Hellhammer J, Hellhammer DH (2005): A new view on hypocortisolism. Psychoneuroendocrinology 30:1010–1016.

Hatzinger M, Z'Brun A, Hemmeter U, Seifritz E, Baumann F, Holsboer-Trachsler E, Heuser IJ (1995): Hypothalamic-pituitary-adrenal system function in patients with Alzheimer's disease. Neurobiol Aging 16:205–209.

Hauger RL, Millan MA, Lorang M, Harwood JP, Aguilera G (1988): Corticotropin-releasing factor receptors and pituitary adrenal responses during immobilization stress. Endocrinology 123:396–405.

Heilig CW, Stromski ME, Blumenfeld JD, Lee JP, Gullans SR (1989): Characterization of the major brain osmolytes that accumulate in salt-loaded rats. Am J Physiol 257:F1108–F1116.

Heim C, Ehlert U, Hellhammer DH (2000): The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 25:1–35.

Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB (2001): Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry 158:575–581.

Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB (2008): The dexamethasone/corticotropin-releasing factor test in men with major depression: Role of childhood trauma. Biol Psychiatry 63:398–405.

Heuser I, Yassouridis A, Holsboer F (1994): The combined dexamethasone/CRH test: A refined laboratory test for psychiatric disorders. J Psychiatr Res 28:341–356.

Hollingshead AB (1965): Two-Factor Index of Social Position. New Haven: Yale University Press.

Holsboer F, Lauer CJ, Schreiber W, Krieg JC (1995): Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology 62:340–347.

Kirschbaum C, Pirke KM, Hellhammer DH (1993): The 'Trier Social Stress Test'—A tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28:76–81.

Kunugi H, Ida I, Owashi T, Kimura M, Inoue Y, Nakagawa S, Yabana T, Urushibara T, Kanai R, Aihara M, Yuuki N, Otsubo T, Oshima A, Kudo K, Inoue T, Kitaichi Y, Shirakawa O, Isogawa K, Nagayama H, Kamijima K, Nanko S, Kanba S, Higuchi T, Mikuni M (2006): Assessment of the dexamethasone/CRH test as a state-dependent marker for hypothalamic-pituitary-adrenal (HPA) axis abnormalities in major depressive episode: A multicenter study. Neuropsychopharmacology 31,212–220.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ (1998): Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci 1:69–73.

Makino S, Gold PW, Schulkin J (1994): Corticosterone effects on corticotropin-releasing hormone mRNA in the central nucleus of the amygdala and the parvocellular region of the paraventricular nucleus of the hypothalamus. Brain Res 640:105–112.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003): An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19:1233–1239.

Maldjian JA, Laurienti PJ, Burdette JH (2004): Precentral gyrus discrepancy in electronic versions of the Talairach atlas. Neuroimage 21:450–455.

Matsunaga H, Sarai M (2000): Low-dose (0.5 mg) DST in manic and major depressive episodes: In relation to the severity of symptoms. Seishin Shinkeigaku Zasshi 102:367–398.

Matsuoka K, Uno M, Kasai K, Koyama K, Kim Y (2006): Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. Psychiatry Clin Neurosci 60:332–339.

Mechelli A, Friston KJ, Frackowiak RS, Price CJ (2005): Structural covariance in the human cortex. J Neurosci 25:8303–8310.

Miller GE, Chen E, Zhou ES (2007): If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol Bull 133:25–45.

Mollica RF, Caspi-Yavin Y, Lavelle J (1996): The Harvard Trauma Questionnaire (HTQ) Manual: Cambodian, Laotian, and Vietnamese Versions Torture 6:19–42.

Mollica RF, Sarajlic N, Chernoff M, Lavelle J, Vukovic IS, Massagli MP (2001): Longitudinal study of psychiatric symptoms, disability, mortality, and emigration among Bosnian refugees. JAMA 286:546–554.

Morris RC, Evendon JL, Sahakian BJ, Robbins TW (1987): Computer-aided assessment of dementia: Comparative studies of neuropsychological deficits in Alzheimer-type dementia and Parkinson's disease. In: Stahl SM, Iversen SD, Goodman EC, editors. Cognitive Neurochemistry. Oxford, United Kingdom: Oxford University Press. pp 21–36.

Murphy E, Brewin CR, Silka L (1997): The assessment of parenting using the parental bonding instrument: Two or three factors? Psychol Med 27:333–341.

Nelson HE (1982): National Adult Reading Test (NART). Windsor: NFER-Nelson.

O'Brien JT, Ames D, Schweitzer I, Colman P, Desmond P, Tress B (1996): Clinical and magnetic resonance imaging correlates of hypothalamic-pituitary-adrenal axis function in depression and Alzheimer's disease. Br J Psychiatry 168:679–687.

Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97–113.

Pariante CM, Miller AH (2001): Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment. Biol Psychiatry 49:391–404.

Parker G, Tupling H, Brown LB (1979): A parental bonding instrument. Br J Med Psychol 52:1–10.

Parker G, Hadzi-Pavlovic D (1992): Parental representations of melancholic and non-melancholic depressives: Examining for specificity to depressive type and evidence for additive effects. Psychol Med 22:657–665.

Pryce CR, Rüedi-Bettschen D, Dettling AC, Weston A, Russig H, Ferger B, Feldon J (2005): Long-term effects of early-life environmental manipulations in rodents and primates: Potential animal models in depression research. Neurosci Biobehav Rev 29:649–674.

Sapolsky RM (1999): Glucocorticoids, stress, and their adverse neurological effects: Relevance to aging. Exp Geront 34:721–732.

Schubert MI, Kalisch R, Sotiropoulos I, Catania C, Sousa N, Almeida OF, Auer DP (2008): Effects of altered corticosteroid milieu on rat hippocampal neurochemistry and structure- an in vivo magnetic resonance spectroscopy and imaging study. J Psychiatr Res 42:902–912.

Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B (1997): Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med 27:951–959.

Swaab DF, Bao A, Lucassen PJ (2005): The stress system in the human brain in depression and neurodegeneration. Age Res Rev 4:141–194.

Tyrka AR, Price LH, Gelernter J, Schepker C, Anderson GM, Carpenter LL (2009): Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: Effects on hypothalamic-pituitary-adrenal axis reactivity. Biol Psychiatry 66:681–685.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289.

Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O, Holden J (1994): Neurotoxicity of glucocorticoids in the primate brain. Horm Behav 28:336–348.

Woon FL, Hedges DW (2008): Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis. Hippocampus 18:729–736.

Yehuda R, Lowy MT, Southwick SM, Shaffer D, Giller EL Jr (1991): Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. Am J Psychiatry 148:499–504.

Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW (1993): Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. Am J Psychiatry 150:83–86.

Zung WWK (1965): A self-rating depression scale. Arch Gen Psychiatry 12:63–70.

PLOS ONE

Mismatch Negativity and Cognitive Performance for the Prediction of Psychosis in Subjects with At-Risk Mental State

Yuko Higuchi[1], Tomiki Sumiyoshi[1]*, Tomonori Seo[1], Tomohiro Miyanishi[1], Yasuhiro Kawasaki[2], Michio Suzuki[1]

1 Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Science, Toyama, Japan, **2** Department of Neuropsychiatry, Kanazawa Medical University, Uchinada-machi, Japan

Abstract

Background: A shorter duration of untreated psychosis has been associated with better prognosis in schizophrenia. In this study, we measured the duration mismatch negativity (dMMN), an event-related potential, and cognitive performance in subjects with at-risk mental state (ARMS), patients with first-episode or chronic schizophrenia, and healthy volunteers. The main interest was to determine if these neurocognitive measures predict progression to overt schizophrenia in ARMS subjects.

Methodology/Principal Findings: Seventeen ARMS subjects, meeting the criteria of the Comprehensive Assessment of At-Risk Mental State, 31 schizophrenia patients (20 first-episode and 11 chronic) and healthy controls (N = 20) participated in the study. dMMN was measured by an auditory odd-ball paradigm at baseline. Neuropsychological performance was evaluated by the Japanese version of the Brief assessment of cognitive function of schizophrenia (BACS-J). The first-episode schizophrenia group showed significantly smaller amplitudes at frontal electrodes than did control subjects whereas chronic patients elicited smaller amplitudes at frontal and central electrodes, consistent with previous reports. During the follow-up period, 4 out of the 17 ARMS subjects transitioned to schizophrenia (converters) while 13 did not (non-converters). Specifically, dMMN amplitudes of non-converters did not differ from those of healthy controls, while converters showed significantly smaller dMMN amplitudes at some electrodes compared to control subjects. Converters performed significantly worse on tests of working memory, verbal fluency, and attention/information processing than did non-converters. There was a significant positive correlation between dMMN amplitudes at the frontal electrodes and verbal fluency, as measured by the BACS, in the AMRS subjects as a whole.

Conclusions/Significance: ARMS subjects who later developed schizophrenia elicited smaller dMMN amplitudes to begin with, compared to non-converters. Notably, we have provided the first evidence for the ability of verbal fluency to predict dMMN amplitudes in ARMS subjects. These findings are expected to add to the efforts for early diagnosis and intervention of schizophrenia.

Citation: Higuchi Y, Sumiyoshi T, Seo T, Miyanishi T, Kawasaki Y, et al. (2013) Mismatch Negativity and Cognitive Performance for the Prediction of Psychosis in Subjects with At-Risk Mental State. PLoS ONE 8(1): e54080. doi:10.1371/journal.pone.0054080

Editor: Tadafumi Kato, RIKEN Brain Science Institution, Japan

Received August 16, 2012; **Accepted** December 5, 2012; **Published** January 17, 2013

Funding: This work was supported by grants-in-aid for Scientific Research from Japan Society for the Promotion of Science, grants-in-aid from the Ministry of Health, Labour and Welfare, Japan, and SENSHIN Medical Research Foundation.The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: tomikisumiyoshi840@hotmail.com

Introduction

Schizophrenia usually develops around the adolescence period, with the whole life risk of about 0.85% [1]. Patients with schizophrenia suffer from positive symptoms (hallucination, delusion, thought disturbance, and etc.), negative symptoms (blunted affect, lack of volition, social withdrawal and etc.), and impairment in a range of cognitive domains, e.g. several types of memory, executive function, attention, verbal fluency [2,3,4,5]. Especially, cognitive function is considered to be a major determinant of outcome, including quality of life and social function [6]. It is interesting that the classification of cognitive domains differs across neuropsychological test batteries. For example, verbal fluency is categorized as an independent domain in the Brief Assessment of Cognition in Schizophrenia (BACS) [7,8], while it is regarded as one of the components of processing speed (of information) in the Measurement and Treatment Research to Improve Cognition in Schizophrenia – Consensus Cognitive Battery [9].

In order to achieve satisfactory long-term outcome, early detection, intervention and treatment of schizophrenia are needed. Specifically, a shorter duration of untreated psychosis (DUP) has been associated with a greater response to antipsychotic drugs in terms of symptoms and quality of life [10]. Prolonged DUP is also associated with decreased levels of social functions, for example, work function and communication skills, as well as longer

Table 1. Demographic and clinical data and dMMN amplitude.

	Healthy controls(n = 20)	ARMS(n = 17)	First episode schizophrenia(n = 20)	Chronic schizophrenia (n = 11)
Male/female	14/6	4/13	9/11	6/5
Age (years)	25.4 (6.9), range 16–45	19.4 (4.4)*, range, 15–29	27.2 (7.3), range 16–38	28.1 (8.0), range 18–44
Age of onset (years)	–	–	26.5 (7.1)	20.2 (4.7)
Duration of illness (years)	–	–	0.65 (0.51)	7.9 (6.9)
Drug dose a)	–	0.1(0.4)	2.1(2.3)	3.2 (2.4)
SAPS	–	13.2 (9.3)	15.7 (13.1)	17.6 (19.1)
SANS	–	50.3 (20.1)	53.8 (25.9)	51.5 (26.1)
dMMN amplitude[μV]				
F3	7.5 (1.3)	7.6 (2.2)	5.3 (1.5) **	4.5 (1.0) **
F4	7.3 (1.2)	7.5 (2.1)	5.6 (1.8) *	5.0 (1.3) **
Fz	7.9 (1.1)	7.9 (2.1)	5.6 (1.7) **	5.1 (1.7) **
Cz	6.6 (1.5)	6.6 (2.2)	5.1 (1.5)	4.2 (1.7) **
Pz	4.5 (1.7)	4.2 (2.0)	3.5 (1.2)	2.5 (1.0) **

Values represent mean (SD).
a) Risperidone equivalent [mg/day].
ARMS, at-risk mental state.
SAPS, Scale for the Assessment of Positive Symptoms;
SANS, Scale for the Assessment of Negative Symptoms.
*$p<0.05$ and ** $p<0.01$, compared to healthy control.
doi:10.1371/journal.pone.0054080.t001

hospitalization [11,12,13,14,15,16,17]. In this context, it was reasonable that recent efforts have been directed to subjects with "at-risk mental state (ARMS)" or "ultra-high risk patients." [18].

For the purpose of early diagnosis, objective biomarkers, particularly, those based on brain morphology, neurophysiology, and neuropsychology have been reported to provide useful information [19,20,21,22,23,24]. Neurophysiological measurements, such as event-related potentials (ERPs), have been suggested to provide a biological substrate for some aspects of cognitive disturbances of schizophrenia. Especially, P300, mismatch negativity (MMN), or N400 etc. are widely used ERPs for this purpose. For example, schizophrenia patients show smaller amplitudes of P300 than normal control subjects [25,26,27]. Reduction of P300 amplitudes has been also noted in subjects with ARMS, part of which develops schizophrenia [28]. P300 has been shown to be affected by various factors, including medication [20,29,30] suggesting the utility as a state marker of psychotic disorders.

MMN is another component of ERPs generated in response to occasional variations (e.g., duration, frequency, intensity) of acoustic stimuli, and is suggested to reflect pre-attentive cognitive operations [31,32]. MMN amplitudes have been shown to be decreased in patients with schizophrenia, as indicated by a recent meta-analysis [33] reporting a large effect size. Unlike the case with P300, MMN amplitudes are generally not affected by psychotropic drug, for example benzodiazepines [34], dopamine antagonists [35]. For these reasons, MMN is considered to provide a trait marker for schizophrenia.

There are several types of MMNs, such as duration MMN (dMMN) and frequency MMN (fMMN), based on the mode of presentation of stimuli. Attenuation of the fMMN amplitude, resulting from changes in the frequency of stimuli, reflects the progress of the disease, i.e. a function of duration of the illness. On the other hand, deficits of dMMN deficiency, resulting from changes in the duration of stimuli, may be more closely linked to the genetic aspect of schizophrenia [36]. Thus, impairment of dMMN is greater than that of fMMN [37], with the latter emerging only in the chronic, but not early stage of schizophrenia [38,39].

Recently, dMMN amplitudes have been shown to be reduced already in the prodromal stage of schizophrenia. Thus, Jahshan et al (2011) found dMMN amplitudes in subjects with at-risk for psychosis patients were reduced compared to normal controls, but the deficits were milder than those in patients with first episode schizophrenia [40]. Atkinson et al (2011) report that dMMN amplitudes were reduced as early as in the ultra-high risk stage [41]. This finding was extended by Bodatsch et al (2011) [42] and Shaikh et al (2012) [43], who observed smaller dMMN amplitudes in drug-naïve subjects with ARMS who later converted to overt psychosis, compared to those in non-converters. Thus, reduced dMMN amplitudes have been regarded to provide a biomarker to predict the development of schizophrenia.

Cognitive impairment, a core symptom of schizophrenia, is present at onset of illness [44], and is closely related to functional outcome [45]. Carrion et al. (2011) observed that cognitive and functional impairments are already evident in ultra-high risk patients before the onset of psychosis. Specifically, attention/processing speed was found to predict progression to psychosis [46]. On the other hand, Frommann et al. (2011) report prodromal patients were impaired in all neurocognitive domains, such as learning memory, executive control, processing speed, and working memory. These findings indicate neuropsychological measures, particularly attention/processing speed, provide another cognitive modality to identify high-risk people vulnerable to developing overt schizophrenia [47].

To date, little information is available about the relationship between neurophysiological indices, e.g. dMMN, and neuropsychological performance. So far, Lin et al (2012) investigated the correlation between neuropsychological performance and MMN amplitudes only in patients with schizophrenia [21]. For example, demonstration of the ability of some measures of neuropsychological performance, e.g. attention/information processing and

Table 2. Comparison between converters and non-converters of ARMS subjects.

	ARMS (n = 17)		Analyze of variance (df = 1,16), Group Effect	
	Non-C. (n = 13)	Conv. (n = 4)	F	p
Male/female	2/11	2/2		
Age [years]	18.5 (3.8), range 15–29	22.3 (5.6), range 17–30		
Drug dose [a)]	–	0.5 (0.7)		
SAPS	11.4 (9.3)	18.0 (8.6)		
SANS	42.9 (15.9)	69.0 (18.4) *		
dMMN amplitude[μV]				
F3	8.2 (2.0)	5.6 (1.7)	3.78	n.s.
F4	8.2 (1.6)	5.2 (1.8)	10.61	0.05
Fz	8.6 (1.6)	5.7 (2.0)	8.25	0.01
Cz	7.3 (1.8)	4.3 (1.7)	8.31	0.01
Pz	4.8 (1.8)	2.4 (1.2)	4.74	0.04
BACS-J				
Verbal memory	51.0 (7.8)	47.2 (11.3)	0.57	n.s.
Working memory	19.1 (3.2)	14.7 (2.2)	6.33	0.02
Motor function	69.3 (12.5)	60.5 (9.0)	1.66	n.s.
Verbal fluency	46.7 (12.1)	29.0 (9.5)	7.03	0.01
Attention	74.0 (12.7)	56.2 (5.8)	7.05	0.01
Executive function	17.8 (2.1)	18.5 (2.6)	0.24	n.s.

Values represent mean (SD).
a) Risperidone equivalent [mg/day].
ARMS, at-risk mental state.
Non-C., ARMS non-converters; Conv., ARMS converters.
SAPS, Scale for the Assessment of Positive Symptoms;
SANS, Scale for the Assessment of Negative Symptoms;
BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese version.
*$p<0.05$ compared to Non-C. (student's t-test).
doi:10.1371/journal.pone.0054080.t002

verbal fluency, to predict dMMN activity would greatly facilitate the early intervention practice, as the former indices require only a limited time constraint. Moreover, such evidence, if obtained, would help more precisely identify biological features of the prodromal phase of schizophrenia.

In this study, we measured dMMN amplitudes and cognitive performance in subjects with ARMS, first episode schizophrenia, or chronic phase of the illness, and compared them with those of normal control subjects. Specifically, we compared the results from ARMS subjects who later developed schizophrenia (converters) and those who did not (non-converters). The hypotheses tested were; 1) if correlations exist between the decrease in dMMN amplitudes and the impairment of neuropsychological performance in subjects with ARMS, and 2) if the impairments of neurophysiological and neuropsychological functions would similarly predict progression to overt psychosis in these subjects.

Methods

Ethics Statement

This protocol was approved by the Committee on Medical Ethics of the University of Toyama. After complete and detail description of the study to the subjects, written informed consent was obtained.

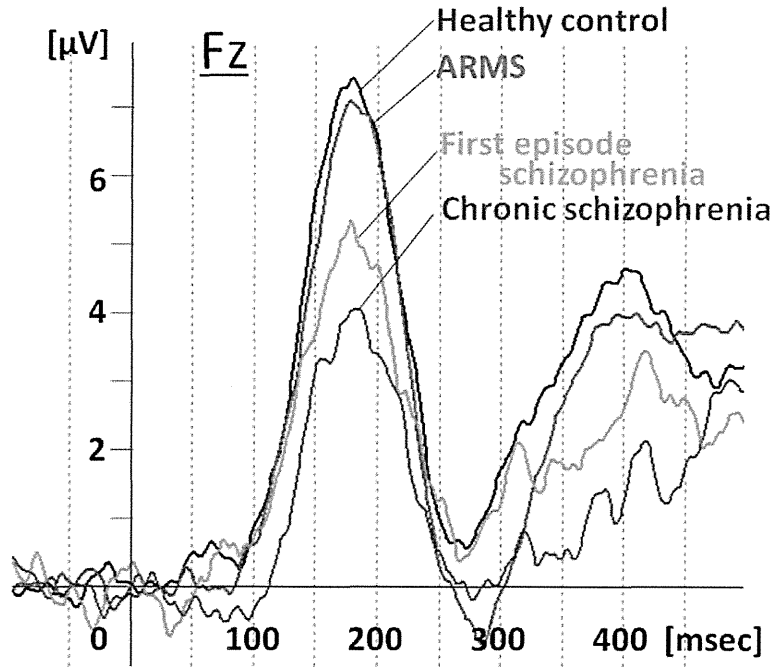
Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in research. If the mental status of a subject was impaired to the point where s/he could not understand these issues, the subject was not approached to be in the research. In case there was a possibility that the capacity of a participant to consent was compromised, an additional consent was obtained from next of kin, care takers, or guardians of such subject.

Participants

Diagnosis was made based on the Structured Clinical Interview for DSM-IV (SCID) for schizophrenia and the Comprehensive Assessment of At-Risk Mental State (CAARMS) for ARMS [48], by experienced psychiatrists. Most of these subjects were referred from "Psychiatric Health and Welfare Center of Toyama (PHWCT). Seventeen ARMS subjects followed at the University of Toyama Hospital participated in this study. [male/female = 4/13; mean (S.D.) age = 19.4(4.4)]. Thirty-one schizophrenia patients also participated in this study. Patients with duration of illness less than two years were defined as first episode schizophrenia (FES) [n = 20; male/female = 9/11; mean (S.D.) age = 27.2(7.3)], while those with duration of illness 2 years or longer were defined as chronic schizophrenia (CS) [n = 11; male/female = 6/5; mean (S.D.) age = 28.1(8.0)]. We recruited normal control subjects from the community by advertisements. They are healthy volunteers [n = 20; male/female = 14/6; mean (S.D.) age = 25.4(6.9)] without any personal history of psychiatric illnesses, including schizophrenia or other psychotic disorders.

All participants were right-handed. A psychiatric and treatment history was obtained from the subjects, families, and medical

A.


[μV]
Fz
Healthy control
ARMS
First episode schizophrenia
Chronic schizophrenia
6
4
2
0
100
200
300
400 [msec]

B.

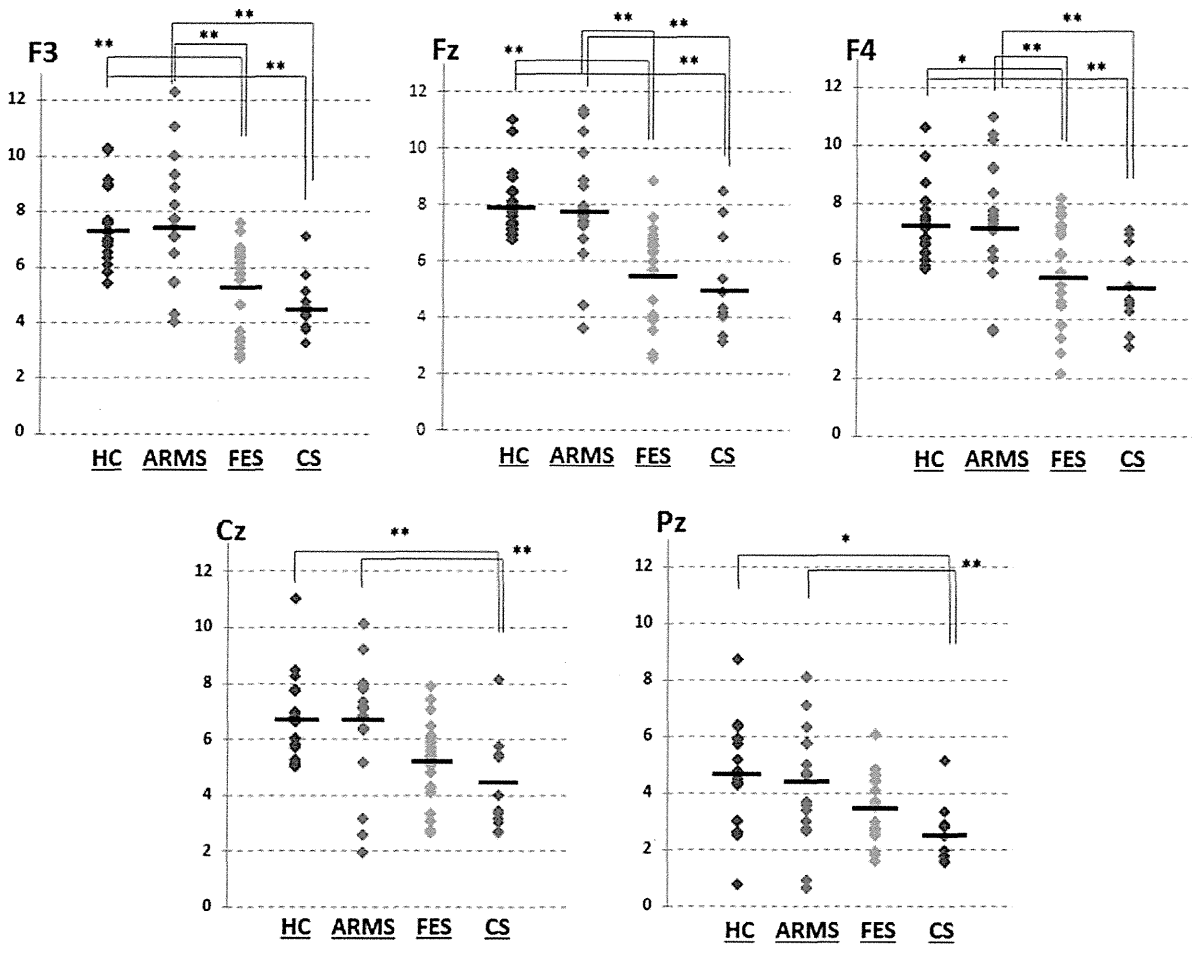

F3
Fz
F4
Cz
Pz
HC ARMS FES CS

Figure 1. Duration mismatch negativity (dMMN) waveform at Fz and scatterplots of dMMN amplitudes for all subjects. A. Waveforms are presented for healthy controls (HC, blue line), at-risk mental state (ARMS, red line), first episode schizophrenia (FES, light green line) and chronic schizophrenia (CS, dark green line). B. Distribution of amplitudes are presented for healthy controls (HC, blue dots), ARMS (red dots), first episode schizophrenia (light green dots) and chronic schizophrenia (dark green dots). * $p<0.05$ and ** $p<0.01$, compared to each groups.
doi:10.1371/journal.pone.0054080.g001

records. Subjects with a current history of substance abuse or dependence, seizure or head injury were excluded from the study. Eligible patients had a complete physical examination and standard laboratory testing was normal. Demographic data at baseline evaluation are shown in Table 1.

ARMS subjects were followed-up continuously at the hospital. Four out of the 17 ARMS subjects transitioned to schizophrenia during the observation period. When DSM-IV criteria were met, e.g. auditory hallucinations persisted or any delusion (for example, disturbance of the self) clearly observed, the subject was regarded to have converted to schizophrenia (converters; Conv.). Subjects who did not develop psychosis were defined as non-converters (Non-C.). The average observation period for ARMS subjects was 2.1±1.1 (Non-C.; 1.6±0.8) years.

Clinical Assessment

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) [49] were administered by an experienced psychiatrist. These data are shown in Table 1.

Neuropsychological Assessments

Neuropsychological performance, measured by the Japanese version of the BACS (BACS-J) [8], was evaluated by experienced psychiatrists or psychologists. The BACS-J cognitive battery uses the following assessments in the respective targeted domains: list learning (verbal memory), digit sequencing task (working memory), token motor task (motor function), category fluency and letter fluency (verbal fluency), symbol coding (attention and processing speed), and the Tower of London test (executive function), as shown in Table 1.

Electroencephalogram Recording

Electroencephalograms (EEGs) were recorded based on the previous report of our laboratory [20,30,50,51,52,53]. A 32-channel DC-amplifier (EEG-2100 version 2.22J,Nihon Kohden Corp., Tokyo, Japan), according to the international 10–20 system was used, and recordings were performed using an electro cap (Electrocap Inc., Eaton, OH) in a sound-attenuated room. Data were collected with a sampling rate of 500 Hz. All electrodes were referred to the average amplitude of the ear electrodes (bandwidth = 0.53–120 Hz, 60 Hz notch filter). Electrode impedance was less than 5 kΩ.

Measurements of dMMN were based on our previous report [53]. One thousand auditory stimuli were delivered binaurally through headphones with inter-stimulus intervals 500 msec. Standard/target tones of 50/100 msec duration were randomly presented with the presentation probability of 0.9/0.1. All tones were 60 dB, 1000 Hz and with a rise-fall time of 10 msec. The subjects were requested to watch silent animation movie (Tom and Jerry) and pay attention to the monitor and ignore the tones.

Averaging of ERP waves and related procedures were performed using Vital Tracer and EPLYZER II software (Kissei Comtec, Co. Ltd. Nagano, Japan). Epochs were 600 msec, including a 100-msec pre-stimulus baseline. Eye movement artifacts (blinks and eye movements) were manually rejected. MMN waveforms were obtained by subtract standard waveforms from target ones. ERP component peaks were identified within the 150–250 msec search windows. We selected F3, F4, Fz, Cz and Pz electrodes for analysis, based on our previous report [49].

Statistical Methods

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 19.0 (SPSS Japan Inc., Tokyo, Japan). In order to investigate group differences in MMN, repeated measures analysis of variance (ANOVA) with electrode site as within-subject variable and diagnostic group as between-subject variable was performed. BACS-J domain scores were analyzed with a two-way ANOVA with BACS-J domains as the within factor and group as the between factor. Group×electrode interactions and group×BACS-J domain score interactions were decomposed using one-way ANOVA, with Bonferroni correction. Relationships between MMN amplitudes at the Fz electrode and BACS -J domain scores were analyzed using Spearman rank correlations.

Raters (psychiatrist, psychologist) were not informed of subjects' profiles and diagnosis.

Results

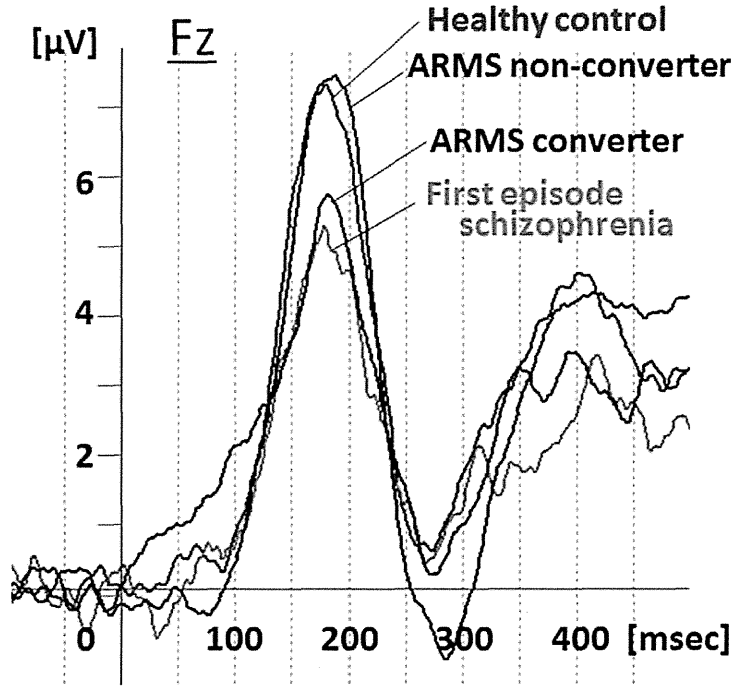
Subjects' Profile

Demographic data of participants are shown in Tables 1 and 2. There was significant group difference in age [$F(3,64)=5.51$, $p=0.02$]. The ARMS group was significantly younger than other groups. The female to male ratio in the ARMS group was significantly greater than that in the normal control group [$\chi^2=7.94$, $p=0.004$]. There was no difference between Conv. and Non-C. in age ($p=0.14$). The male/female ratio of Conv. was greater than Non-C.[$\chi^2=4.41$, $p=0.01$]. Fourteen out of 17 ARMS subjects were not taking any medication, and 3 were prescribed a small dose of risperidone (1.5 mg/day), aripiprazole (6 mg/day), and sulpiride (150 mg/day), respectively, for (or to prevent) acute psychosis episodes (sometimes with strong agitation), based on the criteria of International Early Psychosis Association Writing Group [54]. MMN recordings for these subjects were conducted shortly after medications were started (9, 15 and 27 days). All of the three subjects subsequently developed schizophrenia. Schizophrenia patients were taking the following treatment; FES (no medication 7, risperidone 3, perospirone 3, aripiprazole 2, olanzapine 1, sulpiride 1, blonanserin+quetiapine 1, risperidone+quetiapine 1, risperidone+zotepine 1.), CS (no medication 1, perospirone 3, risperidone 2, olanzapine 2, zotepine 1, perospirone+olanzapine 1, perospirone+aripiprazole 1). There were no differences between ARMS, FES and CS groups in SAPS [$F(2,47)=0.457$, $p=0.636$] and SANS [$F(2,47)=0.118$, $p=0.889$] scores. Conv. and Non-C. groups did not differ in the SAPS score. However, Conv. group showed a significantly higher score of SANS than Non-C. group (69.0±18.4 vs. 42.9±15.9, $p=0.02$).

Comparisons of dMMN Amplitudes between Healthy Controls vs. ARMS vs. Schizophrenia

dMMN data are shown in Table 1 and Figure 1. Grand average waveforms in the Fz lead and scatterplots for the electrodes sites are shown in Figure 1A and 1B. ARMS subjects showed dMMN amplitudes similar to those of healthy control subjects. On the

A.


[μV]
Fz
Healthy control
ARMS non-converter
ARMS converter
First episode schizophrenia
6
4
2
0
100
200
300
400 [msec]

B.

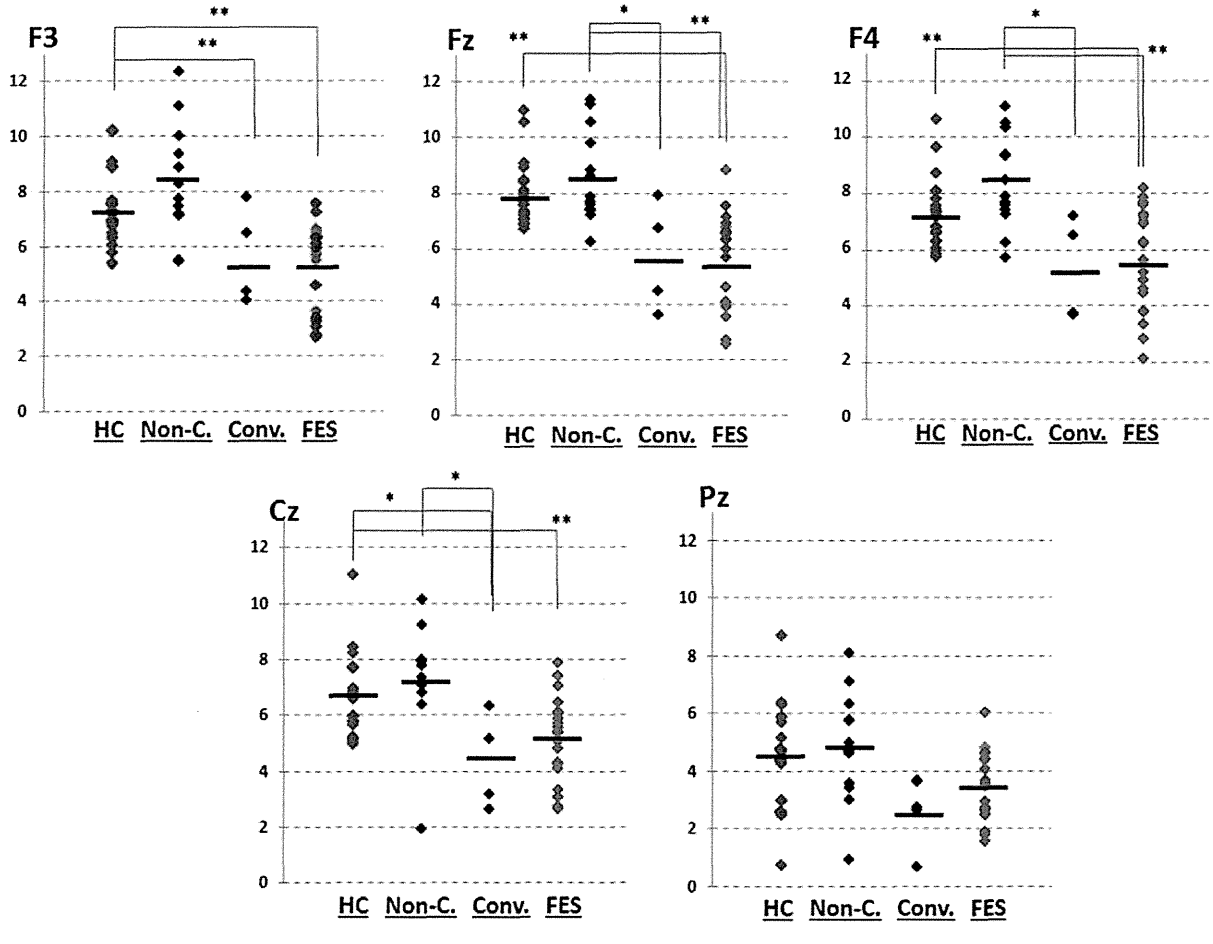

F3
Fz
F4
Cz
Pz
HC Non-C. Conv. FES

Figure 2. dMMN waveform at Fz and scatterplots of dMMN amplitude for at-risk mental state (ARMS,) healthy control (HC) and first episode schizophrenia (FES) subjects. A. Waveforms are presented for healthy controls (blue line), ARMS, converters (Conv.) and non-converter (Non-C.) (black lines), FES (light green line). B. Distribution of amplitudes are presented for healthy controls (blue dots), ARMS, converters (Conv.) and non-converter (Non-C.) (black dots), FES (light green dots). * $p<0.05$ and ** $p<0.01$, compared to each groups.
doi:10.1371/journal.pone.0054080.g002

other hand, FES group showed significantly smaller dMMN amplitudes at frontal electrodes (F3, F4 and Fz). Patients with CS showed greater amplitude reductions at all electrodes compared to healthy controls.

Comparisons of dMMN Amplitudes: Conv. vs. Non-C

Conv. subjects showed significant reduction in dMMN amplitudes at F4, Fz, Cz, and Pz electrode sites compared with Non-C. subjects (Table 2, Figure 2A). Waveforms of Conv. were similar to those of first-episode schizophrenia. By contrast, waveforms of Non-C. resembled to those of healthy controls (Figure 2A). Scatterplots of dMMN amplitudes are shown in Figure 2B. Non-C. subjects elicited larger dMMN amplitudes compared to those of Conv. Amplitudes of Non-C. did not differ from those of healthy controls. On the other hand, Conv. showed significantly smaller dMMN amplitudes at F3 and Cz compared to control subjects. There were no differences in dMMN amplitudes at any electrode between Conv. and FES subjects.

Neuropsychological Measurements: Conv. vs. Non-C

Conv. subjects demonstrated significantly smaller BACS-J scores compared to Non-Conv. subjects for working memory, verbal fluency, and attention (Table 2, Figure 3).

Relationship between Cognitive Performance and dMMN Amplitudes in ARMS subjects

Figure 4 demonstrates correlations between dMMN amplitudes and BACS scores in subjects with ARMS. Significant positive correlations were noted for verbal fluency ($r = 0.546$, $p = 0.02$; Figure 4A), but not other cognitive domains (data not shown). Also, scores of letter fluency task and category fluency task from the BACS-J [55] were significantly correlated with dMMN amplitudes in subjects with ARMS (Figure 4B,C).

Discussion

To our knowledge, this study is the first to report a relationship between dMMN amplitudes and neuropsychological performance in individuals with ARMS. ARMS subjects who later converted to overt schizophrenia elicited reduced dMMN amplitudes at frontal

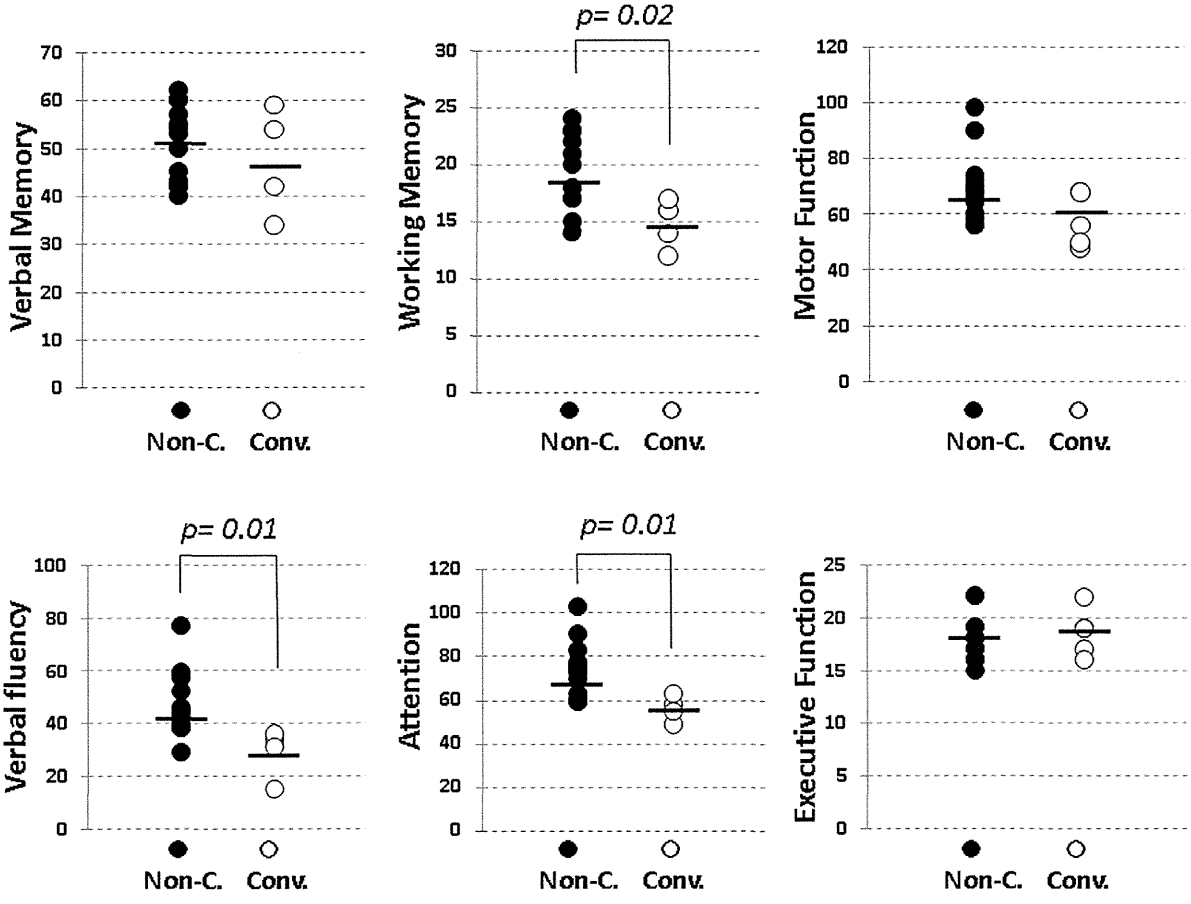


Figure 3. Scatterplot of the score of BACS-J for ARMS subjects. Black symbols(●) and white ones(○) represent scores of non-converters and converters, respectively.
doi:10.1371/journal.pone.0054080.g003

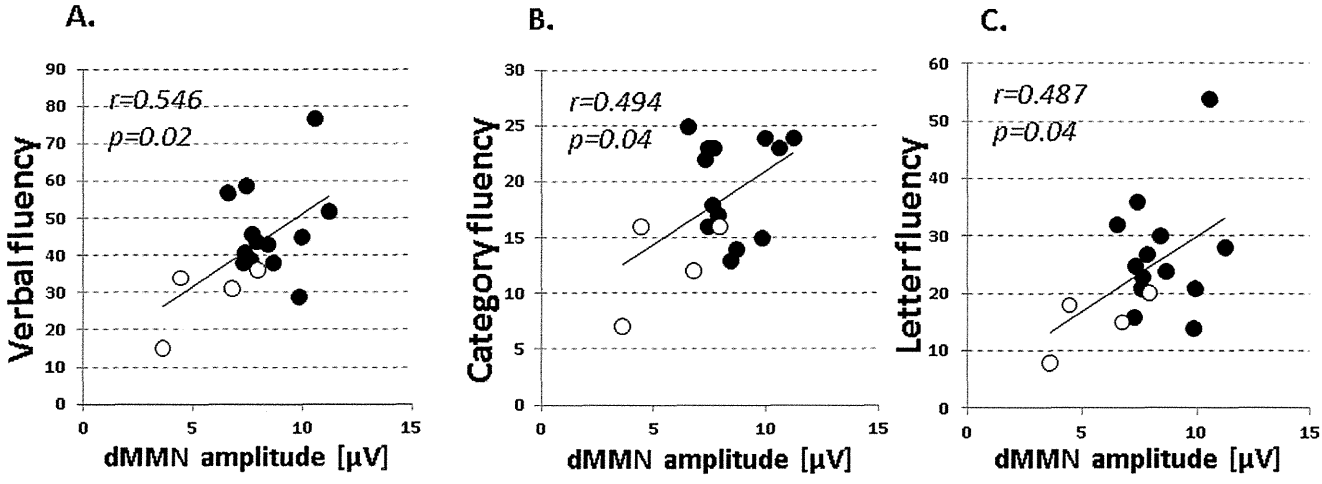


Figure 4. Correlations between dMMN amplitudes at Fz lead and performance on the verbal fluency tasks from the BACS-J in ARMS subjects. Black and white symbols represent scores of non-converters and converters, respectively. Relationships were analyzed using Pearson's product-moment correlation coefficient.
doi:10.1371/journal.pone.0054080.g004

and central leads compared with non-converters and normal subjects, consistent with previous reports [42,43]. In addition, verbal fluency, working memory and attention/information processing were more greatly impaired in converters compared to non-converters at baseline. Further a significant correlation was noted between performance on verbal fluency tasks and dMMN amplitudes in ARMS subjects. First episode schizophrenia patients showed significantly smaller dMMN amplitudes than ARMS subjects and healthy controls, consistent with previous observations [40,56]. Yung et al. (2003) [57] report that 10–40% of ARMS patients develop schizophrenia, consistent with our observations that 4 out of 17 (23.5%) subjects progressed to overt psychosis. Some previous studies report that ARMS subjects elicit reduced dMMN amplitudes, but with a lesser degree compared to patients with established schizophrenia [40,41,42]. By contrast, dMMN amplitudes of the entire ARMS subjects in the present study were not significantly different from those of healthy controls (Figure 1). One of the reasons for this discrepancy is the difference in age and the percentage of gender, as implicated by some previous studies [32,58,59].

The score of SANS/SAPS of ARMS were similar to schizophrenia (Table 1). We consider it was due, mainly, to the nature of the ARMS subjects studied here. Most of these subjects were referred from PHWCT. The PHWCT, a component of the Consultation and Support Service in Toyama(CAST), includes the Local Support Center for Social Withdrawal Young People that advertises its activity using internet home page and pamphlets. These systems mainly receive consultations from the family members of subjects with social withdrawal and/or disability. This may be why the ARMS subjects studied here elicited relatively severe negative symptoms comparable to those in subjects with overt schizophrenia. With regard to SAPS scores, part of the schizophrenia patients in this study had already been medicated, which may have decreased positive symptoms in these subjects. This may make the SAPS scores for ARMS group and schizophrenia groups look somewhat similar.

Compared to non-converters, dMMN amplitudes in converters were significantly reduced at F4, Fz, Cz and Pz leads (Table 2). This finding suggests dMMN amplitudes may be able to differentiate high-risk individuals who convert to schizophrenia from those who do not. Therefore, these electrophysiological findings are expected to facilitate early intervention of schizophrenia.

MMN is a pre-attentional response to a change of stimuli, and plays a critical role in establishing learning and memory. This electrophysiological event has been suggested to be generated by the glutamate (Glu)/N-methyl-D-aspartate (NMDA) system [60]. This theory is supported by the observation that administration of an NMDA-receptor antagonist (phencyclidine, MK-801 etc.) abolishes MMN in monkeys [61] and rats [62,63]. The pathophysiology of schizophrenia has been shown to be associated with the dysfunction of signal transduction through NMDA receptors [64]. Accordingly, Stone et al. (2009) report that ARMS subjects elicited reduced Glu levels in the thalamus, which was correlated with the gray matter volume of frontal and temporal lobes [65], the brain structures suggested to be involved in MMN generation [66,67]. In fact, the results of the present study (Table 2, Figure 2) indicate the ability of diminished dMMN to predict the development of schizophrenia, as in some previous reports [36–39], suggesting impaired NMDA-mediated transmissions provide an endophenotype for subjects vulnerable to the illness.

Neuropsychological deficits have been shown to exist in the early stage of schizophrenia [46,47]. In this study, neuropsychological performance, as measured by the BACS, differentiated between converters and non-converters in ARMS subjects. Compared with non-converters, scores of working memory, verbal fluency and attention in converters were significantly less for converters (Table 2, Figure 3). These results indicate cognitive abilities, particularly those requiring attention/information processing speed, provides a sensitive marker predicting the development of schizophrenia in vulnerable individuals.

The major finding of the present study was the ability of performance on the verbal fluency tasks to predict dMMN amplitudes in subjects with ARMS (Figure 4). The implications of these observations include the possibility of enhancing accuracy to identify subjects diagnosed with "ultra-high risk" who later develop psychosis. Another advantage is that some neuropsychological tests, which only require a shorter time constraint, could substitute for electrophysiological measurements, e.g. ERPs. In fact, verbal fluency test only requires less than 5 minutes. The easiness of assessment would facilitate the screening for subjects whose psychiatric conditions would not allow them to undergo

ERPs measurement, which generally takes more than 30 minutes. On the other hand, neuropsychological evaluations may sometimes be influenced by motivation of examinees. Therefore, combined administration of neurophysiological and neuropsychological assessments would facilitate screening procedures, depending on the condition of patients. In sum, these efforts are likely to lead to improvement of functional outcome for vulnerable subjects through early intervention by objective probes with greater sensitivity and specificity.

In conclusion, this study confirmed that ARMS subjects who later develop schizophrenia elicit smaller dMMN amplitudes to begin with, compared to non-converters. Notably, we have provided the first evidence for the ability of verbal fluency or attention/information processing to predict dMMN amplitudes in ARMS subjects. These findings are expected to add to the efforts for early diagnosis and intervention of schizophrenia.

Limitations

The main limitations of this study include that ARMS subjects were younger and had a larger female/male ratio compared to other groups. Clearly, further study with a larger number of matched subjects is warranted. Part of ARMS subjects was taking antipsychotic drugs which is another limitation of the study.

The observation periods of Non-C. were relatively short (1.6 ± 0.8 year), compared to similar studies [42,43], which might be another limitation.

Author Contributions

Conceived and designed the experiments: YH T. Sumiyoshi. Performed the experiments: YH T. Seo TM. Analyzed the data: YH YK. Contributed reagents/materials/analysis tools: T. Sumiyoshi MS. Wrote the paper: YH T. Sumiyoshi.

References

1. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, et al. (1992) Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychol Med Monogr Suppl 20: 1–97.
2. Meltzer HY, Sumiyoshi T (2003) Atypical antipsychotic drugs improve cognition in schizophrenia. Biol Psychiatry 53: 265–267; author reply 267–268.
3. Sumiyoshi T, Jayathilake K, Meltzer HY (2003) The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. Schizophr Res 59: 7–16.
4. Harvey PD, Green MF, Keefe RS, Velligan DI (2004) Cognitive functioning in schizophrenia: a consensus statement on its role in the definition and evaluation of effective treatments for the illness. J Clin Psychiatry 65: 361–372.
5. Heinrichs RW, Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12: 426–445.
6. Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153: 321–330.
7. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, et al. (2004) The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 68: 283–297.
8. Kaneda Y, Sumiyoshi T, Keefe R, Ishimoto Y, Numata S, et al. (2007) Brief assessment of cognition in schizophrenia: validation of the Japanese version. Psychiatry Clin Neurosci 61: 602–609.
9. Green MF, Nuechterlein KH, Kern RS, Baade LE, Fenton WS, et al. (2008) Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS Psychometric and Standardization Study. Am J Psychiatry 165: 221–228.
10. Perkins DO, Gu H, Boteva K, Lieberman JA (2005) Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry 162: 1785–1804.
11. Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, et al. (1992) Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 149: 1183–1188.
12. Melle I, Larsen TK, Haahr U, Friis S, Johannesen JO, et al. (2008) Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. Arch Gen Psychiatry 65: 634–640.
13. Yamazawa R, Nemoto T, Kobayashi H, Chino B, Kashima H, et al. (2008) Association between duration of untreated psychosis, premorbid functioning, and cognitive performance and the outcome of first-episode schizophrenia in Japanese patients: prospective study. Aust N Z J Psychiatry 42: 159–165.
14. Galderisi S, Mucci A, Bitter I, Libiger J, Bucci P, et al. (2012) Persistent negative symptoms in first episode patients with schizophrenia: Results from the European First Episode Schizophrenia Trial. Eur Neuropsychopharmacol.
15. Chang WC, Hui CL, Tang JY, Wong GH, Lam MM, et al. (2011) Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr Res 133: 22–28.
16. Edwards J, McGorry PD, Waddell FM, Harrigan SM (1999) Enduring negative symptoms in first-episode psychosis: comparison of six methods using follow-up data. Schizophr Res 40: 147–158.
17. Malla AK, Norman RM, Takhar J, Manchanda R, Townsend L, et al. (2004) Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J Nerv Ment Dis 192: 455–463.
18. McGorry PD, Nelson B, Amminger GP, Bechdolf A, Francey SM, et al. (2009) Intervention in individuals at ultra-high risk for psychosis: a review and future directions. J Clin Psychiatry 70: 1206–1212.
19. Kawasaki Y, Suzuki M, Kherif F, Takahashi T, Zhou SY, et al. (2007) Multivariate voxel-based morphometry successfully differentiates schizophrenia patients from healthy controls. Neuroimage 34: 235–242.
20. Higuchi Y, Sumiyoshi T, Kawasaki Y, Matsui M, Arai H, et al. (2008) Electrophysiological basis for the ability of olanzapine to improve verbal memory and functional outcome in patients with schizophrenia: a LORETA analysis of P300. Schizophr Res 101: 320–330.
21. Lin YT, Liu CM, Chiu MJ, Liu CC, Chien YL, et al. (2012) Differentiation of schizophrenia patients from healthy subjects by mismatch negativity and neuropsychological tests. PLoS One 7: e34454.
22. Nakamura K, Kawasaki Y, Suzuki M, Hagino H, Kurokawa K, et al. (2004) Multiple structural brain measures obtained by three-dimensional magnetic resonance imaging to distinguish between schizophrenia patients and normal subjects. Schizophr Bull 30: 393–404.
23. Takayanagi Y, Takahashi T, Orikabe L, Mozue Y, Kawasaki Y, et al. (2011) Classification of first-episode schizophrenia patients and healthy subjects by automated MRI measures of regional brain volume and cortical thickness. PLoS One 6: e21047.
24. Takahashi T, Zhou SY, Nakamura K, Tanino R, Furuichi A, et al. (2011) A follow-up MRI study of the fusiform gyrus and middle and inferior temporal gyri in schizophrenia spectrum. Prog Neuropsychopharmacol Biol Psychiatry 35: 1957–1964.
25. Kawasaki Y, Maeda Y, Higashima M, Nagasawa T, Koshino Y, et al. (1997) Reduced auditory P300 amplitude, medial temporal volume reduction and psychopathology in schizophrenia. Schizophr Res 26: 107–115.
26. Roth WT, Pfefferbaum A, Horvath TB, Berger PA, Kopell BS (1980) P3 reduction in auditory evoked potentials of schizophrenics. Electroencephalogr Clin Neurophysiol 49: 497–505.
27. Bruder GE, Tenke CE, Towey JP, Leite P, Fong R, et al. (1998) Brain ERPs of depressed patients to complex tones in an oddball task: relation of reduced P3 asymmetry to physical anhedonia. Psychophysiology 35: 54–63.
28. Ozgurdal S, Gudlowski Y, Witthaus H, Kawohl W, Uhl I, et al. (2008) Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia. Schizophr Res 105: 272–278.
29. Umbricht D, Javitt D, Novak G, Bates J, Pollack S, et al. (1998) Effects of clozapine on auditory event-related potentials in schizophrenia. Biol Psychiatry 44: 716–725.
30. Sumiyoshi T, Higuchi Y, Itoh T, Matsui M, Arai H, et al. (2009) Effect of perospirone on P300 electrophysiological activity and social cognition in schizophrenia: a three-dimensional analysis with sloreta. Psychiatry Res 172: 180–183.
31. Naatanen R, Paavilainen P, Rinne T, Alho K (2007) The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin Neurophysiol 118: 2544–2590.
32. Naatanen R, Kujala T, Escera C, Baldeweg T, Kreegipuu K, et al. (2012) The mismatch negativity (MMN)–a unique window to disturbed central auditory processing in ageing and different clinical conditions. Clin Neurophysiol 123: 424–458.
33. Umbricht D, Krljes S (2005) Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res 76: 1–23.
34. Kasai K, Yamada H, Kamio S, Nakagome K, Iwanami A, et al. (2002) Do high or low doses of anxiolytics and hypnotics affect mismatch negativity in schizophrenic subjects? An EEG and MEG study. Clin Neurophysiol 113: 141–150.
35. Leung S, Croft RJ, Baldeweg T, Nathan PJ (2007) Acute dopamine D(1) and D(2) receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. Psychopharmacology (Berl) 194: 443–451.
36. Naatanen R, Kahkonen S (2009) Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. Int J Neuropsychopharmacol 12: 125–135.
37. Michie PT, Budd TW, Todd J, Rock D, Wichmann H, et al. (2000) Duration and frequency mismatch negativity in schizophrenia. Clin Neurophysiol 111: 1054–1065.
38. Todd J, Michie PT, Schall U, Karayanidis F, Yabe H, et al. (2008) Deviant matters: duration, frequency, and intensity deviants reveal different patterns of

mismatch negativity reduction in early and late schizophrenia. Biol Psychiatry 63: 58–64.
39. Salisbury DF, Shenton ME, Griggs CB, Bonner-Jackson A, McCarley RW (2002) Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. Arch Gen Psychiatry 59: 686–694.
40. Jahshan C, Cadenhead KS, Rissling AJ, Kirihara K, Braff DL, et al. (2012) Automatic sensory information processing abnormalities across the illness course of schizophrenia. Psychol Med 42: 85–97.
41. Atkinson RJ, Michie PT, Schall U (2012) Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol Psychiatry 71: 98–104.
42. Bodatsch M, Ruhrmann S, Wagner M, Muller R, Schultze-Lutter F, et al. (2011) Prediction of psychosis by mismatch negativity. Biol Psychiatry 69: 959–966.
43. Shaikh M, Valmaggia L, Broome MR, Dutt A, Lappin J, et al. (2012) Reduced mismatch negativity predates the onset of psychosis. Schizophr Res 134: 42–48.
44. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, et al. (1994) Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry 51: 124–131.
45. Green MF, Kern RS, Heaton RK (2004) Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res 72: 41–51.
46. Carrion RE, Goldberg TE, McLaughlin D, Auther AM, Correll CU, et al. (2011) Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. Am J Psychiatry 168: 806–813.
47. Frommann I, Pukrop R, Brinkmeyer J, Bechdolf A, Ruhrmann S, et al. (2011) Neuropsychological profiles in different at-risk states of psychosis: executive control impairment in the early–and additional memory dysfunction in the late–prodromal state. Schizophr Bull 37: 861–873.
48. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, et al. (2005) Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 39: 964–971.
49. Andreasen NC (1990) Methods for assessing positive and negative symptoms. Mod Probl Pharmacopsychiatry 24: 73–88.
50. Itoh T, Sumiyoshi T, Higuchi Y, Suzuki M, Kawasaki Y (2011) LORETA analysis of three-dimensional distribution of delta band activity in schizophrenia: relation to negative symptoms. Neurosci Res 70: 442–448.
51. Sumiyoshi T, Higuchi Y, Kawasaki Y, Matsui M, Kato K, et al. (2006) Electrical brain activity and response to olanzapine in schizophrenia: a study with LORETA images of P300. Prog Neuropsychopharmacol Biol Psychiatry 30: 1299–1303.
52. Kawasaki Y, Sumiyoshi T, Higuchi Y, Ito T, Takeuchi M, et al. (2007) Voxel-based analysis of P300 electrophysiological topography associated with positive and negative symptoms of schizophrenia. Schizophr Res 94: 164–171.
53. Higuchi Y, Sumiyoshi T, Kawasaki Y, Ito T, Seo T, et al. (2010) Effect of tandospirone on mismatch negativity and cognitive performance in schizophrenia: a case report. J Clin Psychopharmacol 30: 732–734.
54. International Early Psychosis Association Writing Group (2005) International clinical practice guidelines for early psychosis. Br J Psychiatry Suppl 48: s120–124.
55. Kaneda Y, Sumiyoshi T, Nakagome K, et al. (2008) The brief assessment of cognition in schizophrenia Japanese version (BACS-J). Seishin Igaku 50: 913–917.
56. Kaur M, Battisti RA, Ward PB, Ahmed A, Hickie IB, et al. (2011) MMN/P3a deficits in first episode psychosis: comparing schizophrenia-spectrum and affective-spectrum subgroups. Schizophr Res 130: 203–209.
57. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, et al. (2003) Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res 60: 21–32.
58. Ikezawa S, Nakagome K, Mimura M, Shinoda J, Itoh K, et al. (2008) Gender differences in lateralization of mismatch negativity in dichotic listening tasks. Int J Psychophysiol 68: 41–50.
59. Matsubayashi J, Kawakubo Y, Suga M, Takei Y, Kumano S, et al. (2008) The influence of gender and personality traits on individual difference in auditory mismatch: a magnetoencephalographic (MMNm) study. Brain Res 1236: 159–165.
60. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, et al. (2000) Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. Arch Gen Psychiatry 57: 1139–1147.
61. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC (1996) 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 93: 11962–11967.
62. Tikhonravov D, Neuvonen T, Pertovaara A, Savioja K, Ruusuvirta T, et al. (2008) Effects of an NMDA-receptor antagonist MK-801 on an MMN-like response recorded in anesthetized rats. Brain Res 1203: 97–102.
63. Eriksson J, Villa AE (2005) Event-related potentials in an auditory oddball situation in the rat. Biosystems 79: 207–212.
64. Brzustowicz LM, Simone J, Mohseni P, Hayter JE, Hodgkinson KA, et al. (2004) Linkage disequilibrium mapping of schizophrenia susceptibility to the CAPON region of chromosome 1q22. Am J Hum Genet 74: 1057–1063.
65. Stone JM, Day F, Tsagaraki H, Valli I, McLean MA, et al. (2009) Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. Biol Psychiatry 66: 533–539.
66. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, et al. (2007) Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. Schizophr Bull 33: 69–94.
67. Opitz B, Rinne T, Mecklinger A, von Cramon DY, Schroger E (2002) Differential contribution of frontal and temporal cortices to auditory change detection: fMRI and ERP results. Neuroimage 15: 167–174.

PLOS ONE

LORETA Current Source Density for Duration Mismatch Negativity and Neuropsychological Assessment in Early Schizophrenia

Tomohiro Miyanishi, Tomiki Sumiyoshi*, Yuko Higuchi, Tomonori Seo, Michio Suzuki

Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan

Abstract

Introduction: Patients with schizophrenia elicit cognitive decline from the early phase of the illness. Mismatch negativity (MMN) has been shown to be associated with cognitive function. We investigated the current source density of duration mismatch negativity (dMMN), by using low-resolution brain electromagnetic tomography (LORETA), and neuropsychological performance in subjects with early schizophrenia.

Methods: Data were obtained from 20 patients meeting DSM-IV criteria for schizophrenia or schizophreniform disorder, and 20 healthy control (HC) subjects. An auditory odd-ball paradigm was used to measure dMMN. Neuropsychological performance was evaluated by the brief assessment of cognition in schizophrenia Japanese version (BACS-J).

Results: Patients showed smaller dMMN amplitudes than those in the HC subjects. LORETA current density for dMMN was significantly lower in patients compared to HC subjects, especially in the temporal lobes. dMMN current density in the frontal lobe was positively correlated with working memory performance in patients.

Conclusions: This is the first study to identify brain regions showing smaller dMMN current density in early schizophrenia. Further, poor working memory was associated with decreased dMMN current density in patients. These results are likely to help understand the neural basis for cognitive impairment of schizophrenia.

Citation: Miyanishi T, Sumiyoshi T, Higuchi Y, Seo T, Suzuki M (2013) LORETA Current Source Density for Duration Mismatch Negativity and Neuropsychological Assessment in Early Schizophrenia. PLoS ONE 8(4): e61152. doi:10.1371/journal.pone.0061152

Editor: Kenji Hashimoto, Chiba University Center for Forensic Mental Health, Japan

Received November 22, 2012; **Accepted** March 6, 2013; **Published** April 5, 2013

Funding: This work was supported by grants-in-aid for Scientific Research from Japan Society for the Promotion of Science, grants-in-aid from the Ministry of Health, Labour and Welfare, Japan, and SENSHIN Medical Research Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: tomikisumiyoshi840@hotmail.com

Introduction

Schizophrenia is a chronic and progressive psychotic disorder that emerges mainly in late adolescence or early adulthood. Patients with the illness exhibit positive symptoms and negative symptoms, as well as disturbances of various domains of cognitive function, e.g. verbal memory, working memory, executive function, and attention [1,2]. In particular, cognitive impairments have been shown to disturb their social activities, work outcome, and quality of life. Recent studies [3,4] report that mild cognitive deficits already exist before the onset of schizophrenia, or "at risk mental state" (ARMS). The neural substrates for cognitive deficits may include some brain regions, such as hippocampus and parahippocampal gyrus [5–8].

Mismatch negativity (MMN) is one of the event-related potentials (ERPs) generated by a deviant (infrequent) stimulus. MMN is elicited even under pre-attentive conditions, and reflects an automatic pre-attention process. Generation of the MMN is an indicator of auditory sensory memory, and represent information processing dependent on some components of the auditory cortex, e.g. superior temporal gyrus [9–11]. Previous studies using low-resolution brain electromagnetic tomography (LORETA), fMRI, and other procedures have demonstrated that MMN reflects activities of a neural network involving several brain structures. Among them, the auditory cortex plays a key role in the complex neural architecture of sensory discrimination [12–14].

The feature of MMN waveforms varies according to type of deviant stimuli, i.e. frequency, duration, intensity, and location. For example, diminished MMN amplitudes reflect cognitive decline in psychiatric conditions [15]. In schizophrenia, smaller amplitudes of MMN, especially duration MMN (dMMN), have been reported [3,16–19].

Several attempts have been made to relate MMN amplitudes and neuropsychological performance [17–21]. Lin et al. used predictive multivariate logistic regression model, and demonstrated dMMN and performance IQ, evaluated by the Wechsler Adult Intelligence Scale-Third Edition, can distinguish between schizophrenia patients and healthy control (HC) subjects [22].

LORETA provides three-dimensional images of brain electrical activity [23]. There are only a few reports on LORETA analysis of MMN in schizophrenia. Park et al. (2002) [24] observed a significant decrease in the current density for frequency MMN in the left superior temporal gyrus and left inferior parietal gyrus in patients with schizophrenia. Recently, Takahashi et al (2013)

report reduced dMMN current density at right medial frontal gyrus, right cingulate gyrus, and right paracentral lobule in patients with chronic schizophrenia [12]. To our knowledge, there is no report on LORETA analysis of dMMN in early psychosis.

The above considerations indicate the ability of the combination of neuropsychological tests and dMMN to provide an objective measure to diagnose schizophrenia. So far, no study has investigated the correlation between MMN current density in some brain regions, e.g. frontal lobe, and neuropsychological performance.

Therefore, this study was conducted to test the hypotheses that 1) patients with schizophrenia would exhibit decreased dMMN current density in brain areas relevant to the pathophysiology of the illness, such as some temporal lobe structures [25], and 2) reduced dMMN current density in the frontal lobe would be associated with impairment of neuropsychological performance, such as working memory.

Methods

Ethics Statement

This protocol was approved by the Committee on Medical Ethics of the University of Toyama. After a complete and detail description of the study was given, subjects provided written informed consent. Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in this research. If the mental status of a subject was impaired to the point where s/he could not understand these issues, the subject was not asked to participate in this research. If there was a possibility that the capacity of a participant to consent was compromised, an additional consent form was obtained from the next of kin, care takers, or guardians of such subjects.

Participants

Subjects were diagnosed by experienced psychiatrists, based on the Structured Clinical Interview for DSM-IV (SCID) for schizophrenia or schizophreniform disorder. Twenty patients (male/female, 9/11; mean [S.D.] age, 27.2 [7.3]) participated in this study. Their duration of illness was less than 2 years. Twenty HC participants (male/female, 14/6; mean [S.D.] age, 25.4 [6.9]) were also recruited. They had no personal history of psychiatric illnesses, including schizophrenia and other psychotic disorders. All participants were right-handed. Psychiatric and treatment histories were obtained from the subjects, family members, and medical records. Subjects with a current history of substance abuse or dependence, seizure, or head injury were excluded from the study. Complete physical examination revealed no neurological illness for all subjects. Demographic data at baseline evaluation are shown in Table 1.

Clinical and neurocognitive assessment

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) [26] were administered by an experienced psychiatrist. These data are shown in Table 1.

Neuropsychological performance, measured by the brief assessment of cognition in schizophrenia Japanese version (BACS-J) [27], was evaluated by experienced psychiatrists or psychologists. The BACS-J uses the following assessments in the respective targeted domains; list learning (verbal memory), digit sequencing task (working memory), token motor task (motor function), category fluency and letter fluency (verbal fluency), symbol coding (attention and processing speed), and the Tower of London test (executive function) [27], as shown in Table 1. These scores were transformed into Z-scores using data from healthy volunteers, as previously reported [27,28]. Raters were not informed of subjects' profiles or their diagnoses.

Table 1. Demographic and clinical data.

	Healthy controls (n = 20)	Early schizophrenia (n = 20)
Male/Female	14/6	9/11
Age (years)	25.4 (6.9)	27.2 (7.3)
	range, 16–45	range, 16–38
Education (years)	15.1 (2.9)	13.2 (2.1) *
Age at onset (years)	-	26.5 (7.1)
Duration of illness (years)	-	0.6 (0.5)
Antipsychotic dose (Risperidone equivalent mg/day)	-	2.1 (2.4)
SAPS	-	16.5 (13.2)
SANS	-	53.9 (25.2)
BACS-J (Z-score)#		
Verbal memory		−1.22 (1.59)
Working memory		−1.16 (1.18)
Motor function		−2.52 (1.07)
Verbal fluency		−1.12 (0.77)
Attention		−1.65 (0.75)
Executive function		−0.40 (1.89)

Values represent means (SD).
SAPS, Scale for the Assessment of Positive Symptoms.
SANS, Scale for the Assessment of Negative Symptoms.
BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese version.
*p<0.05, significantly smaller than healthy controls.
SD unit compared to reported values (ref. [27,28]).
doi:10.1371/journal.pone.0061152.t001

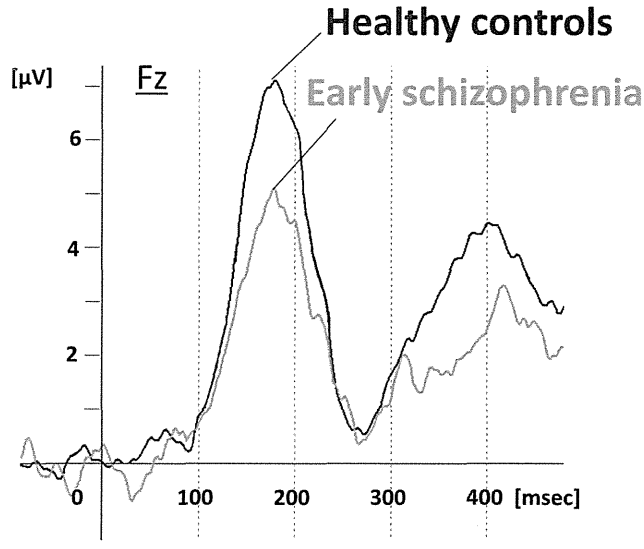


Figure 1. Duration mismatch negativity (dMMN) waveforms at the Fz lead. dMMN waveforms for healthy controls (N = 20, blue line) and early schizophrenia (N = 20, light green line) are shown.
doi:10.1371/journal.pone.0061152.g001

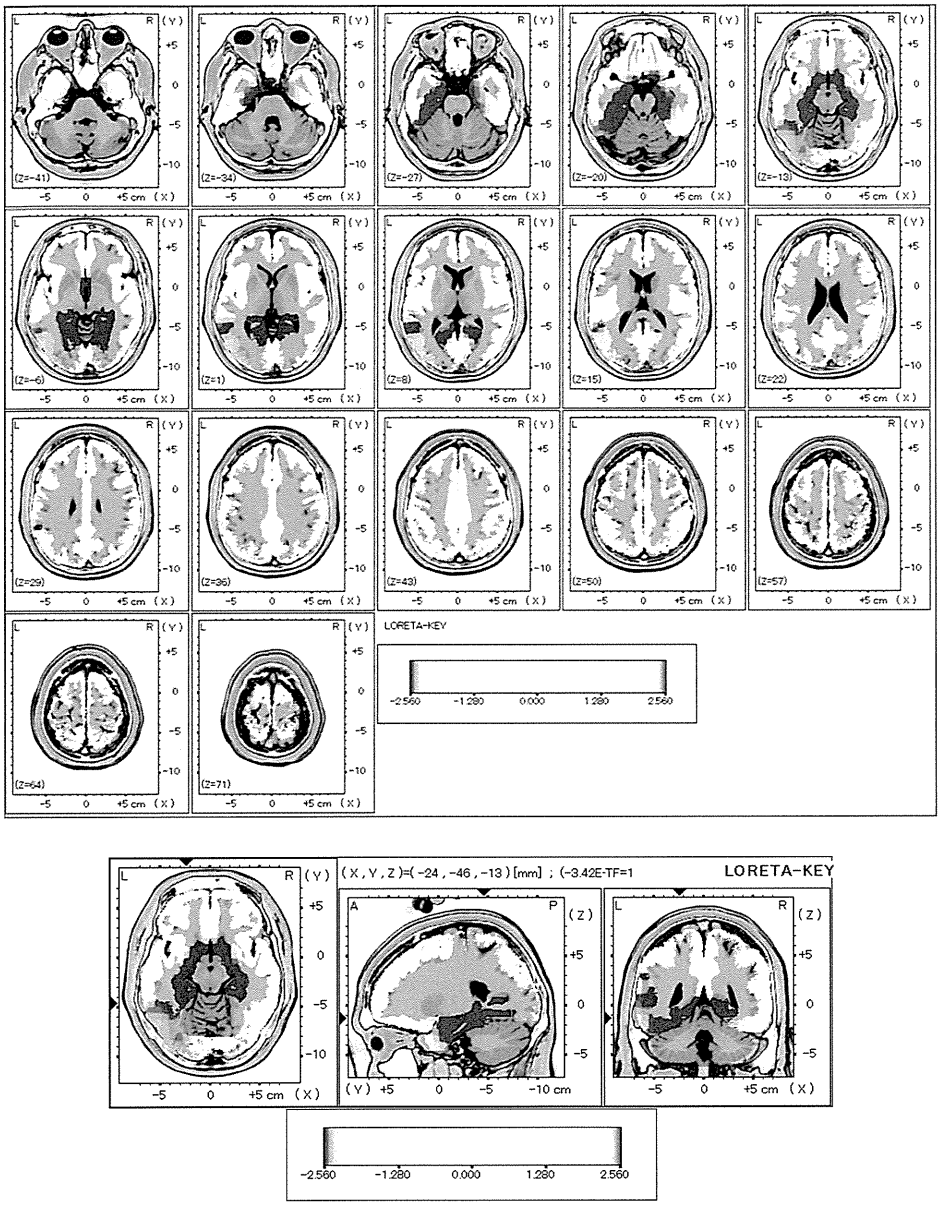


Figure 2. LORETA images for dMMN. Comparison of LORETA current density for dMMN between early schizophrenia (N = 20) and healthy control (N = 20, HC) subjects, as revealed by statistical non-parametric mapping voxel-wise comparison for independent samples. Blue areas represent brain regions showing significantly lower LORETA values for early schizophrenia subjects in comparison with HC subjects.
doi:10.1371/journal.pone.0061152.g002

Electroencephalographic recording

Electroencephalograms (EEGs) were recorded based on previous reports from our laboratory [29–34]. A 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kohden Corp., Tokyo, Japan), according to the international 10–20 system, was used. Recordings were performed using an electro cap (Electro cap Inc., Eaton, OH) in a sound-attenuated room. Data were collected with a sampling rate of 500 Hz. All electrodes were referred to the average amplitude of the ear electrodes (bandwidth, 0.53–120 Hz, 60 Hz notch filter). Electrode impedance was less than 5 kΩ. Measurements of dMMN were based on our previous report [33]. One thousand auditory stimuli were delivered binaurally through headphones with inter-stimulus intervals of 500 ms. Standard/target tones of 50/100 ms duration were randomly presented with a presentation probability of 0.9/0.1. All tones were 60 dB, 1000 Hz and with a rise-fall time of 10 ms. Subjects were requested to watch a silent animated movie (Tom and Jerry®), and to pay attention to the monitor and ignore the tones. Averaging of ERP waves and related procedures were performed using Vital Tracer and EPLYZER II software (Kissei Comtec, Co. Ltd. Nagano, Japan). Epochs were 600 ms, including a 100-ms pre-stimulus baseline. Eye movement artifacts (blinks and eye movements) were manually rejected. MMN waveforms were obtained by subtracting the standard waveforms from the target waveforms. ERP component peaks were identified within the fixed search windows between 100–250 ms. We confirmed the presence of the peaks of MMN in all subjects.

LORETA analysis

LORETA images were obtained by estimating the current source density distribution for epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution applied to the digitized Talairach and Tournoux (1988) [35], based on the established method [23]. LORETA made use of the three-shell spherical head model registered to the Talairach atlas available as a digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle et al (1993) [36]. The solution space was restricted to cortical gray matter and the hippocampus, as determined by the corresponding digitized Probability Atlas also available from the Brain Imaging Centre. A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33% [23]. We used the original LORETA version reported by Pascual-Marqui et al [23]. We calculated LORETA images for each subject in the fixed time frame between the 100–250 ms post-stimulus period to obtain the LORETA value for each voxel. Additionally, we averaged LORETA value containing the following brain regions of interest (ROI): frontal lobe, temporal lobe, parietal lobe, and occipital lobe.

Data analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20 (SPSS Japan Inc., Tokyo, Japan). To investigate differences between groups, dMMN amplitudes at the Fz lead were assessed by independent t-test. Comparisons between early schizophrenia and HC on LORETA source imaging were conducted using voxel-by-voxel unpaired *t*-statistics after logarithmic transformation of the data. Holmes' non-parametric correction for multiple comparisons was applied [37]. Relationships of LORETA current density with BACS-J domain scores, SAPS total scores, and SANS total scores were analyzed using Spearman rank correlations. Bonferroni correction was applied for multiple comparisons. LORETA current density for dMMN did not show a uniformly normal distribution. Therefore, dMMN current density was subjected to natural logarithmic transformation to obtain a more normal distribution. The significance level for all statistical tests was set at $p<0.05$ (two-tailed).

Results

Subjects' profiles

Demographic data of participants are shown in Table 1. The female to male ratio and age were not significant between patients and HC (data not presented). Education level was significantly lower in patients than in HC subjects ($t = 2.29$; $p = 0.028$).

Neuropsychological assessments

BACS data for patients are shown in Table 1. Except for executive function, the Z-scores of the other domains were below −1.0. Especially motor function was severely impaired.

Comparisons of dMMN amplitudes between HC and early schizophrenia

Figure 1 shows the overall average dMMN waveforms in the Fz lead. dMMN amplitudes in HC and patients (mean ± SD) were 7.9±1.1 μV and 5.6±1.7 μV, respectively. Patients showed significantly smaller dMMN amplitudes than did HC subjects ($t = 4.97$; $p<0.01$).

Table 2. Coordinates for brain areas showing the largest differences (top five) between healthy controls and early schizophrenia in dMMN current density.

		(X,Y,Z)	P-value
①	left parahippocampal gyrus	−24, −46, −13	<0.01
②	left fusiform gyrus	−31, −46, −6	<0.01
③	right parahippocampal gyrus	11, −39, 1	<0.05
④	right hippocampus	25, −39, 1	<0.05
⑤	left anterior cingulate	−3, −11, −6	<0.05

doi:10.1371/journal.pone.0061152.t002

Comparison of LORETA images for dMMN between HC and early schizophrenia

We compared LORETA current source density of dMMN between HC and early schizophrenia. Compared to HC subjects, patients elicited a significantly lower current density in several brain regions, especially those in the temporal lobes, such as parahippocampal gyrus and hippocampus (Figure 2). Additionally, dMMN current density in the frontal structures, such as anterior cingulate, was significantly lower for early schizophrenia. Table 2 demonstrates brain areas showing the largest difference in dMMN current density.

Relationship between psychotic symptoms and LORETA current density for dMMN

There was no significant correlation between the SAPS or SANS score vs. LORETA current density for dMMN in any brain region (data not presented).

Relationship between neuropsychological assessment and dMMN current density

Table 3 demonstrates the relationships between BACS-J domain scores and LORETA current density for dMMN. dMMN current density in the frontal lobe was positively correlated with working memory in patients with early schizophrenia (Table 3,

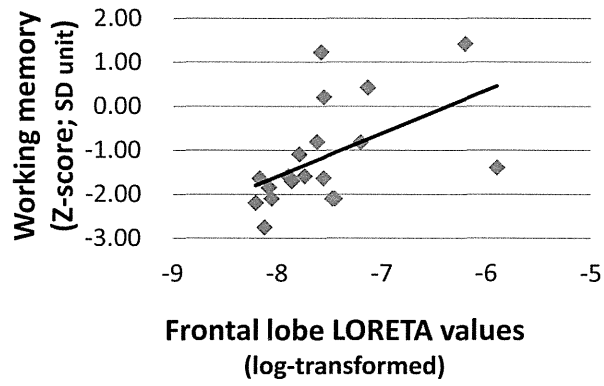


Figure 3. Correlations between dMMN current density and working memory. Scatterplots and least squares regression lines are shown for the correlations between LORETA current density for dMMN (log-transformed) and neuropsychological performance in early schizophrenia.

doi:10.1371/journal.pone.0061152.g003

Table 3. Spearman correlation coefficients between dMMN current density (log-transformed) in discrete brain regions and BACS-J scores in early schizophrenia.

	verbal memory		working memory		motor function		verbal fluency		attention		executive function	
	r	P	r	P	r	P	r	P	r	P	r	P
Frontal lobe	0.308	0.199	0.587	**0.008**	−0.102	0.678	−0.275	0.254	0.097	0.691	−0.092	0.707
Temporal lobe	0.259	0.285	0.448	0.055	−0.220	0.366.	−0.244	0.314	0.116	0.637	−0.108	0.659
Parietal lobe	0.110	0.655	0.274	0.257	−0.146	0.551	−0.256	0.290	0.150	0.540	−0.221	0.364
Occipital lobe	0.072	0.770	0.336	0.160	−0.100	0.683	0.107	0.663	0.372	0.117	0.028	0.909

doi:10.1371/journal.pone.0061152.t003

Figure 3). The correlation remained significant even after Bonferroni correction was applied. There were no such correlations for temporal, parietal, and occipital lobes.

Discussion

To our knowledge, this is the first study to report three-dimensional distribution patterns of dMMN current density and neuropsychological performance in early schizophrenia in comparison with healthy controls. LORETA images demonstrated a decreased dMMN current density in brain areas known to be associated with the pathophysiology of the illness, e.g. parahippocampal gyrus, hippocampus, fusiform gyrus, and anterior cingulate [5,6,38,39]. We also observed positive correlations between dMMN current density in the frontal lobe and working memory performance in patients with early schizophrenia.

Reductions in the volume of several brain regions, including frontal cortex and temporal cortex, in schizophrenia subjects and individuals vulnerable to developing the illness have been reported [40–42]. Reduced dMMN current density in the temporal lobe of patients, observed in this study, is consistent with these morphological findings. Specifically, MMN has been considered to be generated by neural activities in the superior temporal cortex and frontal cortex [9–11]. The present data from a more feasible and non-invasive methodology (i.e. EEG) add support to these lines of evidence for the potential role of several discrete brain regions in the pathophysiology of schizophrenia.

Takahashi et al. (2013) report schizophrenia patients demonstrated a smaller dMMN current density in the right medial frontal gyrus [12]. Compared with our data, their results indicate more frontal regions are affected in patients [12]. The discrepancy may be due to the difference in duration of illness. The subjects of Takahashi's study were chronic schizophrenia, with a mean duration of illness of 23.6 years, while that of our subjects was shorter, i.e. less than 2 years. It is possible that the electrophysiological impairment, e.g. dMMN, becomes more extensive as psychosis progresses. In this context, further study is needed to examine a longitudinal course of dMMN in schizophrenia.

Correlations between MMN amplitudes and neuropsychological performance have been an issue for intensive investigations. Several [17–21], but not all [3,22] studies found MMN amplitudes to be related to cognitive function. The present study revealed, for the first time, that dMMN current density in early schizophrenia was correlated with working memory. Perlstein et al. [43] report that this cognitive domain was associated with dorsolateral prefrontal cortex function, as measured by fMRI, consistent with our electrophysiological findings. Further study should clarify sub-region(s) of the frontal cortex whose dMMN current density is specifically associated with working memory.

The limitations of the present study should be noted. Patients with early schizophrenia were taking antipsychotic drugs which are agonists at dopamine receptors, although modulations of dopaminergic transmission have been shown to exert little effect on dMMN [44,45]. Another limitation may be the use of the original version of LORETA. Further study is warranted to examine dMMN in drug-naïve subjects using an updated version of LORETA (e.g. eLORETA, sLORETA), which would be more advantageous for sub-region analyses and/or multiple comparisons.

In conclusion, this study provides, for the first time, information on the brain regions responsible for diminished dMMN amplitudes in subjects with early schizophrenia. Further, we have found associations between poor working memory and decreased dMMN current density in these patients. These results are likely to help understand the neural basis for cognitive impairment of schizophrenia.

Author Contributions

Conceived and designed the experiments: TM T. Sumiyoshi YH. Performed the experiments: TM YH T. Seo. Analyzed the data: TM T. Sumiyoshi YH. Contributed reagents/materials/analysis tools: TM T. Sumiyoshi YH T. Seo MS. Wrote the paper: TM T. Sumiyoshi YH.

References

1. Elvevåg B, Goldberg T (2000) Cognitive impairment in schizophrenia is the core of the disorder. Crit Rev Neurobiol 14: 1–21.
2. Green MF, Kern RS, Braff DL, Mintz J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "Right stuff"? Schizophr Bull 26: 119–136.
3. Brockhaus-Dumke A, Tendolkar I, Pukrop R, Schultze-Lutter F, Klosterkötter J, et al. (2005) Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. Schizophr Res 73: 297–310.
4. Keefe RS, Perkins DO, Gu H, Zipursky RB, Christensen BK, et al. (2006) A longitudinal study of neurocognitive function in individuals at-risk for psychosis. Schizophr Res 88: 26–35.
5. Sumiyoshi T, Sumiyoshi C, Nohara S, Hagino H, Hasegawa S, et al. (2006) Verbal memory deficits in a preadolescent case of lesions of the left parahippocampal gyrus associated with a benign tumor. Prog Neuropsychopharmacol Biol Psychiatry 30: 733–736.
6. Sumiyoshi T, Tsunoda M, Uehara T, Tanaka K, Itoh H, et al. (2004) Enhanced locomotor activity in rats with excitotoxic lesions of the entorhinal cortex, a neurodevelopmental animal model of schizophrenia: behavioral and in vivo microdialysis studies. Neurosci Lett 364: 124–129.
7. Krabbendam L, Derix M, Honig A, Vuurman E, Havermans R, et al. (2000) Cognitive Performance in Relation to MRI Temporal Lobe Volume in Schizophrenic Patients and Healthy Control Subjects. J Neuropsychiatry Clin Neurosci 12: 251–256.

8. Szeszko PR, Strous RD, Goldman RS, Ashtari M, Knuth KH, et al. (2002) Neuropsychological correlates of hippocampal volumes in patients experiencing a first episode of schizophrenia. Am J Psychiatry 159: 217–226.
9. Giard MH, 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.
10. Mondragón-Maya A, Bernal-Hernández J, Yáñez-Téllez G, Rodríguez-Agudelo Y (2011) Mismatch Negativity (MMN) and schizophrenia: a revision. Actas Esp Psiquiatr 39: 363–373.
11. Alho K (1995) Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear Hear 16: 38–51.
12. Takahashi H, Rissling AJ, Pascual-marqui R, Kirihara K, Pela M, et al. (2013) NeuroImage Neural substrates of normal and impaired preattentive sensory discrimination in large cohorts of nonpsychiatric subjects and schizophrenia patients as indexed by MMN and P3a change detection responses. NeuroImage 66: 594–603.
13. Kircher TT, Rapp A, Grodd W, Buchkremer G, Weiskopf N, et al. (2004) Mismatch negativity responses in schizophrenia: a combined fMRI and whole-head MEG study. Am J Psychiatry 161: 294–304.
14. Shin KS, Kim JS, Kang D, Koh Y, Choi J, et al. (2009) Pre-Attentive Auditory Processing in Ultra-High-Risk for Schizophrenia with Magnetoencephalography. Biol Psychiatry 65: 1071–1078.
15. Näätänen R, Kujala T, Kreegipuu K, Carlson S, Escera C, et al. (2011) The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing. Brain 134: 3435–3453.
16. Shelley A, Ward PB, Catts S V, Michie PT, Andrews S, et al. (1991) Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. Biol Psychiatry 30: 1059–1062.
17. Light GA, Braff DL (2005) Stability of Mismatch Negativity Deficits and Their Relationship to Functional Impairments in Chronic Schizophrenia. Am J Psychiatry 162: 1741–1743.
18. Hermens DF, Ward PB, Hodge MA, Kaur M, Naismith SL, et al. (2010) Impaired MMN/P3a complex in first-episode psychosis: cognitive and psychosocial associations. Prog Neuropsychopharmacol Biol Psychiatry 34: 822–829.
19. Wynn JK, Sugar C, Horan WP, Kern R, Green MF (2010) Mismatch negativity, social cognition, and functioning in schizophrenia patients. Biol Psychiatry 67: 940–947.
20. Toyomaki A, Kusumi I, Matsuyama T, Kako Y, Ito K, et al. (2008) Tone duration mismatch negativity deficits predict impairment of executive function in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 32: 95–99.
21. Rasser PE, Schall U, Todd J, Michie PT, Ward PB, et al. (2011) Gray matter deficits, mismatch negativity, and outcomes in schizophrenia. Schizophr Bull 37: 131–140.
22. Lin YT, Liu CM, Chiu MJ, Liu CC, Chien YL, et al. (2012) Differentiation of schizophrenia patients from healthy subjects by mismatch negativity and neuropsychological tests. PLoS ONE 7: e34454.
23. Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MCG, et al. (1999) Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Res 90: 169–179.
24. Park H, Kwon JS, Youn T, Pae JS, Kim JJ, et al. (2002) Statistical parametric mapping of LORETA using high density EEG and individual MRI: application to mismatch negativities in schizophrenia. Hum Brain Mapp 17: 168–178.
25. Mechelli A, Riecher-Rössler A (2011) Neuroanatomical Abnormalities That Predate the Onset of Psychosis. Arch Gen Psychiatry 68: 489–495.
26. Andreasen NC (1990) Methods for assessing positive and negative symptoms. Mod Probl Pharmacopsychiatry 24: 73–88.
27. Kaneda Y, Sumiyoshi T, Keefe R, Ishimoto Y, Numata S, et al. (2007) Brief assessment of cognition in schizophrenia: validation of the Japanese version. Psychiatry Clin Neurosci 61: 602–609.
28. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, et al. (2004) The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 68: 283–297.
29. Sumiyoshi T, Higuchi Y, Kawasaki Y, Matsui M, Kato K, et al. (2006) Electrical brain activity and response to olanzapine in schizophrenia: a study with LORETA images of P300. Prog Neuropsychopharmacol Biol Psychiatry 30: 1299–1303.
30. Sumiyoshi T, Higuchi Y, Itoh T, Matsui M, Arai H, et al. (2009) Effect of perospirone on P300 electrophysiological activity and social cognition in schizophrenia: a three-dimensional analysis with sLORETA. Psychiatry Res 172: 180–183.
31. Kawasaki Y, Sumiyoshi T, Higuchi Y, Ito T, Takeuchi M, et al. (2007) Voxel-based analysis of P300 electrophysiological topography associated with positive and negative symptoms of schizophrenia. Schizophr Res 94: 164–171.
32. Higuchi Y, Sumiyoshi T, Kawasaki Y, Matsui M, Arai H, et al. (2008) Electrophysiological basis for the ability of olanzapine to improve verbal memory and functional outcome in patients with schizophrenia: a LORETA analysis of P300. Schizophr Res 101: 320–330.
33. Higuchi Y, Sumiyoshi T, Seo T, Miyanishi T., Kawasaki Y. et al. (2013) Mismatch negativity and cognitive performance in the prediction of transition to psychosis in subjects with at risk mental state. PLoS ONE 8:e54080.
34. Itoh T, Sumiyoshi T, Higuchi Y, Suzuki M, Kawasaki Y (2011) LORETA analysis of three-dimensional distribution of delta band activity in schizophrenia: Relation to negative symptoms. Neurosci Res 70: 442–448.
35. Talairach J, Tournoux P (1988) Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.
36. Towle VL, Bolaños J, Suarez D, Tan K, Grzeszczuk R, et al. (1993) The spatial location of EEG electrodes: locating the best-fitting sphere relative to cortical anatomy. Electroencephalogr Clin Neurophysiol 86: 1–6.
37. Holmes AP, Blair RC, Watson JD, Ford I (1996) Nonparametric analysis of statistic images from functional mapping experiments. J Cereb Blood Flow Metab 16: 7–22.
38. Nestor PG, Onitsuka T, Gurrera RJ, Niznikiewicz M, Frumin M, et al. (2007) Dissociable contributions of MRI volume reductions of superior temporal and fusiform gyri to symptoms and neuropsychology in schizophrenia. Schizophr Res 91: 103–106.
39. Fujiwara H, Hirao K, Namiki C, Yamada M, Shimizu M, et al. (2007) Anterior cingulate pathology and social cognition in schizophrenia: a study of gray matter, white matter and sulcal morphometry. NeuroImage 36: 1236–1245.
40. Suzuki M, Zhou SY, Takahashi T, Hagino H, Kawasaki Y, et al. (2005) Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. Brain 128: 2109–2122.
41. Chan RC, Di X, McAlonan GM, Gong Q yong (2011) Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. Schizophr Bull 37: 177–188.
42. Kuroki N, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, et al. (2006) Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. Am J Psychiatry 163: 2103–2110.
43. Perlstein WM, Carter CS, Noll DC, Cohen JD (2001) Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am J Psychiatry 158: 1105–1113.
44. Leung S, Croft RJ, Baldeweg T, Nathan PJ (2007) Acute dopamine D(1) and D(2) receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. Psychopharmacology 194: 443–451.
45. Rissling AJ, Braff DL, Swerdlow NR, Hellemann G, Rassovsky Y, et al. (2012) Disentangling early sensory information processing deficits in schizophrenia. Clin Neurophysiol 123: 1942–1949.