を用いた予備的検討を行った。

1．目　的

統合失調症圏患者の脳機能に対するNEAR（6ヵ月間）の影響の予備的検討として，NEAR実施群において以下の検討を行った。

①認知矯正療法（NEAR）が脳機能に及ぼす影響を，作業記憶課題施行時の脳血液量変化を指標として，多チャンネル近赤外線スペクトロスコピー（NIRS）を用いて測定する。

②神経認知機能や精神症状に対するNEARの効果をアウトカムとする場合の，効果予測因子としてのNIRSデータの有用性を検討する。

2．対象と方法

a．対象者

鳥取大学医学部附属病院に通院中で，13～65歳，IQ＞70，物質依存や頭部外傷の既往がない，という基準を満たし，DSM-Ⅳで統合失調症または統合失調感情障害と診断された患者をNEAR群と対照群の2群に分けて検討した。なお，本研究は，鳥取大学医学部倫理委員会が承認し，すべての被験者に対して事前に研究の趣旨について十分な説明を行い，書面にて同意を得た。

・NEAR群：NEARを6ヵ月間実施した統合失調症圏患者16名（統合失調症13名，統合失調感情障害3名）。なお，PANSSは12名のみのデータ。患者背景を表に示す。

b．検査に使用した評価尺度とスケジュール

NEAR導入前と修了後（約6ヵ月後）の2回，下記の検査を施行：

①統合失調症認知機能簡易評価尺度日本語版（BACS-J）[9]

②陽性・陰性症状評価尺度（PANSS）（引用）[10]

③NIRS：作業記憶課題である2-back課題施行時の脳血液量変化

c．NIRS施行時の認知課題

作業記憶課題である2-back課題によって生じる脳血液量変化をNIRSで測定した。本研究に用いた課題は，図1に示すように，各60秒の課題前，後のベースラインでの0-back課題，および60秒の本課題である2-back課題から成る。ベースラインでの0-back課題では，モニター上に数字「0～9」のいずれかが1つずつ提示され，「9」が提示された場合にのみ，被験者に右手示指でボタン押しを求める。2-back課題では，同様に1つずつ数字が提示されるが，被験者には，提示された数字が2つ前と同じ場合にのみボタン押しを求める（例，5-1-5）。各条件下では25の数字が提示され，その内5つを標的と設定した。

行動指標として下記の3つのパラメータを用いた。

①reaction time

②accuracy：標的に反応した回数/呈示された標的の総数

③sensitivity A'

$= 0.5 + (HR - FAR) \times (1 + HR - FAR) / [4HR \times (1 - FAR)]$

ここで，HR＝標的に対する反応率，FAR＝非標

表　NEAR参加者・臨床背景

NEAR修了人数（16名）	
診断	統合失調症13名，統合失調感情障害3名
性別	男：7　女：9
年齢	27.5±6.9歳
教育年数	13.9±2.0年
発症前推定IQ（JART）	98.9±10.0
罹病期間	5.1±4.3年
発症年齢	22.4±5.6歳
非定型抗精神病薬CP換算	597.6±349.9（NEAR開始時）　566.1±310.7（NEAR修了後）
薬物療法	単剤14人/多剤2人

・鳥取大学医学部附属病院に通院中の統合失調症/統合失調感情障害患者

・16名（修了者）（NEAR治療前後薬物量は，3人減量，3人増量，その他変更なし）

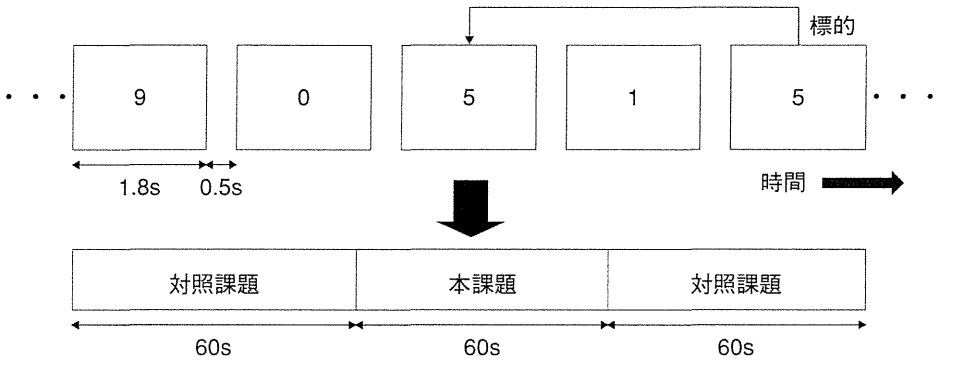


図1　作業記憶課題（2-back課題）
＊本課題では，1つずつ提示される数字列のうち，2つ前と同じ数字が提示された場合に被験者にボタン押しを求める。対象課題では数字“9”が提示された場合にボタン押しを求める。
＊対照課題は，同じ刺激提示条件で“9”がtarget。

的に対する反応率を示す。

d. NIRS計測

NIRS計測には52チャンネル装置（ETG-4000，日立メディコ社製）を用いて，695nm，830nmの2波長の近赤外線によって，［oxy-Hb］および［deoxy-Hb］の相対的変化を修正Lambert則に基づいて，大脳皮質内の各チャンネルで計測した。測定プローブの最下段が国際10-20法のFp1とFp2上となるように設置した（図2）。これによって，背外側（Brodmann area 9：BA 9，BA 46），腹外側（BA 44，45），前頭極（BA 10）の前頭前皮質，および側頭皮質（BA21，22）に相当する皮質領域での測定が可能である（図2）。データのサンプリングタイムは0.1秒とした。本課題前および本課題後のベースラインは，本課題前ベースラインの終わり10秒，本課題後ベースラインの初め5秒の各時間区間の平均値とした。アーチファクト除去目的に，5秒間の移動平均法，およびTakizawaら[15]が開発した半自動式のアーチファクト除去法を適用した。

e. データ解析

認知機能，精神症状は，対応のあるt検定でNEAR実施前後の比較を行った。行動指標はWilcoxon符号付順位和検定でNEAR実施前後の比較を行った。また，作業記憶課題による脳機能の活性化で生じた脳血液量の変化は，チャンネル毎に，作業記憶による脳血液量変化＝（本課題中の［oxy-Hb］平均値－本課題前および後のベースライン［oxy-Hb］平均値）を求め，対応のあるt検定を用いて，この指標のNEAR実施前後の比較を行った。ただし，false discovery rate（FDR）による多重比較補正は実施しなかった。

ベースラインでの作業記憶課題関連［oxy-Hb］，またはNEAR前後の作業記憶課題関連［oxy-Hb］の変化分と，BACS-Jで評価した認知機能あるいはPANSSで評価した精神症状に関するNEAR前後での各指標の変化分との関係について，Spearmanの順位相関で検討した。

3．結　果

a. NEARによる認知機能の変化（図2）

NEAR施行後，BACS-Jの下位6項目のうち，言語記憶［zスコアの改善＋1.0，対応のあるt検定 $p<0.005$，（以下同様）］，運動速度（＋0.88，$p<0.005$），注意（＋0.38，$p<0.05$），遂行機能（＋0.56，$p<0.05$）の4項目は，統計的に有意な改善を示したが，作業記憶（＋0.16，$p=0.34$），語流暢性（＋0.12，$p=0.39$）は変化しなかった。標準化した下位6項目の平均値であるcomposite scoreは有意に改善した（＋0.51，$p<0.001$）。

b. NEARによる精神症状の変化

PANSS陽性尺度はNEAR後に有意に改善したが（対応のあるt検定，$p<0.05$，$N=12$），総得点，陰性および総合精神病理尺度は変化しなかった（対応のあるt検定，$p>0.3$，$N=12$）。

c. NIRS計測

①2-back課題関連の脳血液量変化（図3）

6ヵ月間のNEAR施行後，図3に示すように，左右半球の皮質内10チャンネルで作業記憶課題関連の［oxy-Hb］活性化は有意に増加した（対応のあ

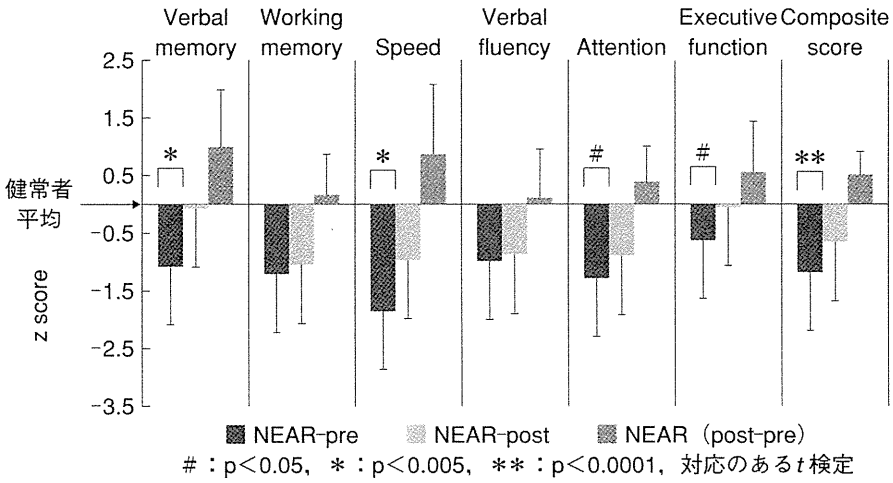


図2　認知機能に対するNEARの効果

16名の統合失調症圏の患者に対する，6ヵ月間のNEARの神経認知機能に対する効果。BACS-Jの6つの下位項目について，健常者340名の平均値と標準偏差を利用して求めた各z-scoreとその平均値であるcomposite score：NEAR施行前（左），施行後（中央），改善度（右）。

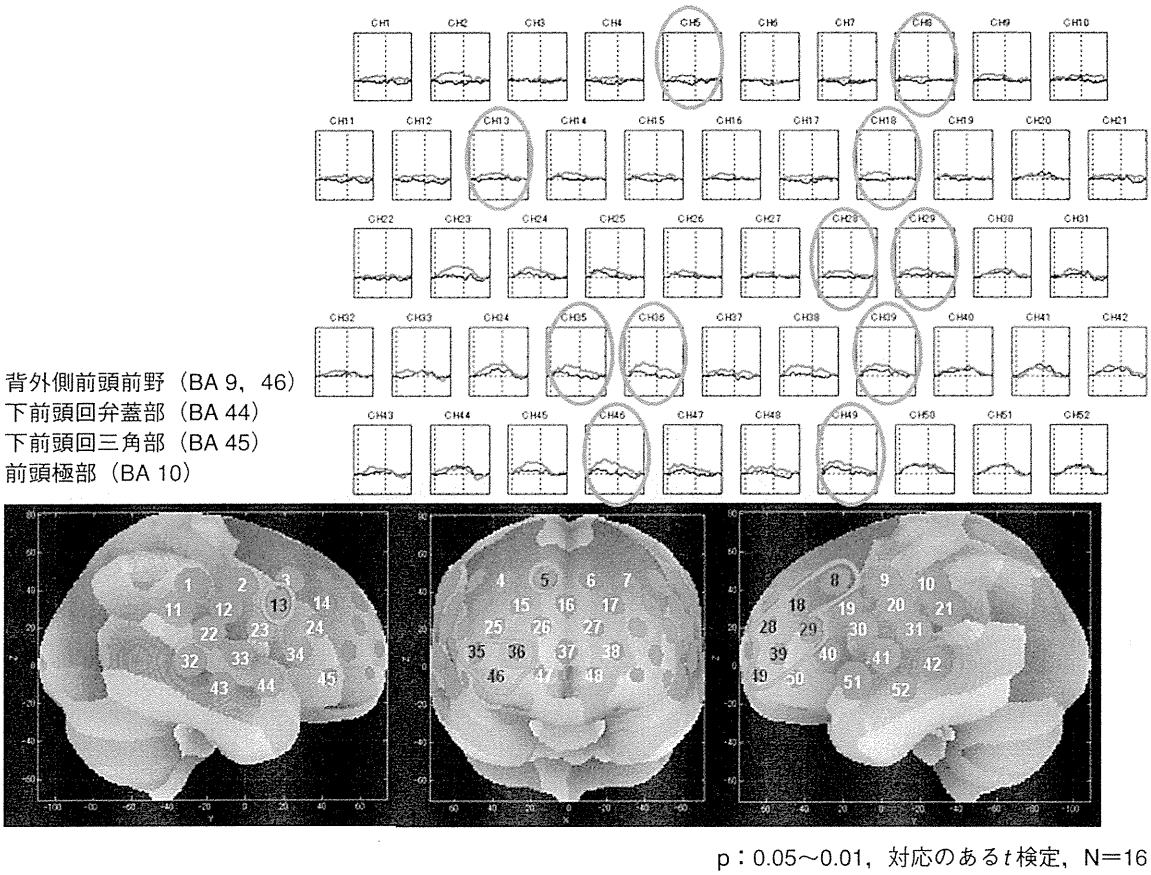
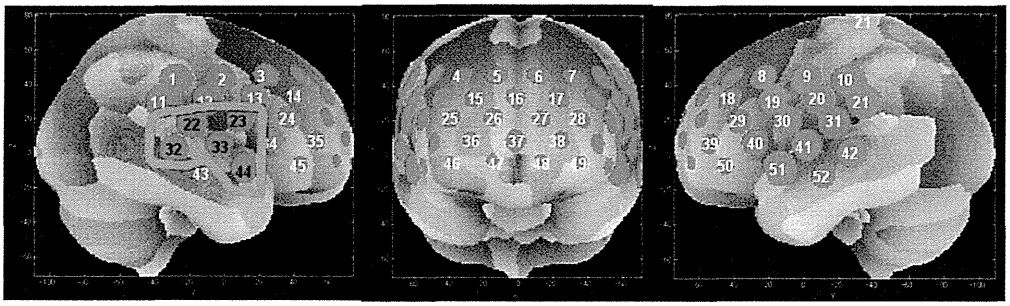
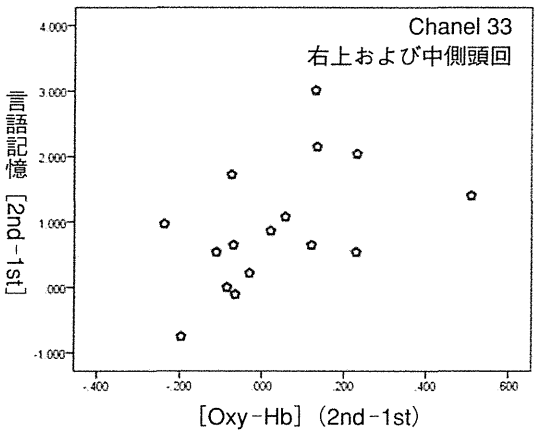


図3　2-back課題関連の［oxy-Hb］活性化がNEAR後に増加した皮質領域

上段：2-back課題施行時の各チャンネルにおける，NEAR前（青）および後（赤）の［oxy-Hb］平均波形（N＝16）。NEAR後に［oxy-Hb］が有意に増加したチャンネルを青丸で標識。下段：NEAR後に［oxy-Hb］が有意に増加した皮質領域を青線で標識。数字はNIRS装置のチャンネルを示す。

るt検定，$p < 0.01 \sim 0.05$，N＝16）。これらの皮質領域は，主に左右背外側前頭前野（BA 9，46），左腹外側前頭前野（BA 45，Broca野），左右前頭極部（BA 10）であった。

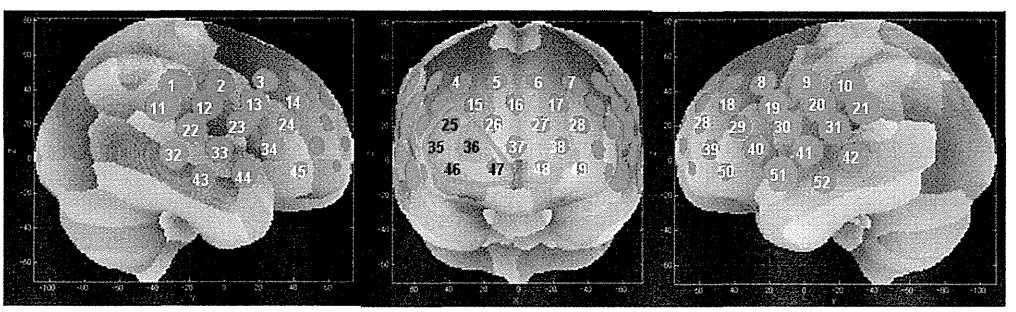


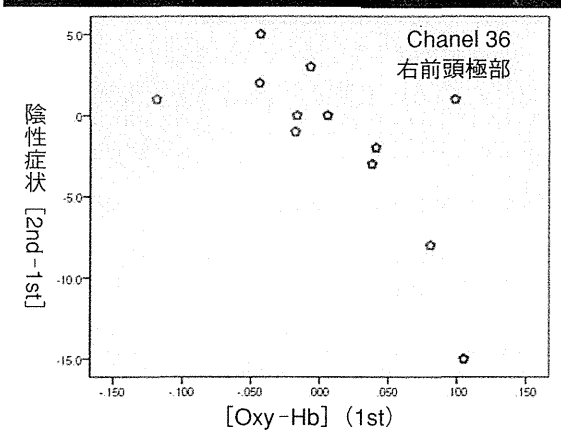


Rho：0.54～0.62；p：0.05～0.01
Spearman's correlation　N＝16

前運動野（BA 6）
中側頭皮質（BA 21）
上側頭皮質（BA 22）
側頭極部（BA 38）
（すべて右半球）

図4　言語記憶の改善と2-back課題関連［oxy-Hb］活性化度の変化との関係
上段：NEAR後のBACS-J言語記憶の改善度が2-back課題関連［oxy-Hb］活性度の変化と正の相関を示した皮質領域を青線で標識。数字はNIRS装置のチャンネルを示す。下段：チャンネル33（右上および中側頭回）での相関。Rho＝0.54（Spearman's correlation，$p < 0.05$，N＝16）。





Rho：-0.68～-0.59；p＜0.05
Spearman's correlation，N＝12

背外側前頭前野（BA 46）
前頭極部（BA 10）
眼窩前頭野（BA 11）

図5　NEAR前の2-back課題関連［oxy-Hb］活性化度とPANSS陰性尺度改善度の関係
上段：NEAR前の2-back課題関連［oxy-Hb］活性化度とNEARによるPANSS陰性尺度の改善度（NEAR後の得点-NEAR前の得点）が負の相関を示した皮質領域を青線で標識。数字はNIRS装置のチャンネルを示す。下段：チャンネル36（右前頭極部）での相関。Rho＝-0.62（Spearman's correlation，$p < 0.05$，N＝12）

②NIRSデータと認知機能，精神症状との相関

NEAR前後のBACS-Jの言語記憶の変化と作業記憶課題関連の［oxy-Hb］活性化の変化が，右半球内の5チャンネルで有意な正の相関を認めた（図4，Spearman's Rho 0.54～0.62，$p < 0.01$～0.05，N＝16）。相関が認められた皮質領域は，運動前野（BA 6），上および中側頭皮質（BA 21，22），側頭極部（BA 38）であった。また，NEAR前後のBACS-Jの語流暢性の変化と作業記憶課題関連の［oxy-Hb］活性化の変化が，やはり主に右半球内の8チャンネルで有意な正の相関を認めた（Spearman's Rho 0.54～0.74，$p < 0.01$～0.05，N＝16）。相関が認められた皮質領域は，運動前野（BA 6），背外側前頭前野（BA 9，46），腹外側前頭前野（BA 45，Broca野），前頭極部（BA 10）であった。BACS-Jの他の4項目，すなわち，作業記憶，運動速度，注意，遂行機能ではNEAR前後の変化と2-back課題関連の［oxy-Hb］活性化の変化は相関しなかった。

精神症状と脳血液量変化との関係では，NEAR前後のPANSS陰性尺度の改善とNEAR開始前のベースラインでの作業記憶課題関連の［oxy-Hb］活性化が，同様に右半球内の5チャンネルで有意な負の相関を示した（図5，Spearman's Rho -0.68～-0.59，$p < 0.05$，N＝12）。相関が認められた皮質領域は，背外側前頭前野（BA 46），前頭極部（BA 10），眼窩前頭前野（BA 11）であった。これに対して，PANSS陽性尺度，同総合精神病理尺度のNEAR前後の変化とベースラインでの作業記憶課題関連の［oxy-Hb］活性化との間には有意な相関を認めなかった（Spearman's Rho -0.14～0.11，$p > 0.24$，N＝12）。

③2-back課題実施時の行動指標

reaction time，accuracy，sensitivity A'の3つの行動指標は，いずれもNEAR前後で変化しなかった（N＝16）。

4．考　察

本研究では，認知矯正療法の一手法であるNEARが脳機能に与える効果について，NIRSを用いて予備的に検討した。前頭前野および側頭皮質の外側面を記録対象とする52チャンネルNIRS装置を用いて，統合失調症圏の患者に対する6ヵ月間のNEARが，一部の皮質領域において，2-back課題という作業記憶課題に関連する［oxy-Hb］活性化の増加という可塑的変化をもたらす可能性があることを示した。NEARによる活性化が認められた皮質領域は，左右背外側前頭前野（BA 9，46），左腹外側前頭前野（BA 45，Broca野），左右前頭極部（BA 10）であった。加えて，2-back課題関連の［oxy-Hb］活性化のNEAR前後での増加程度と神経認知機能の改善度が関連することが，BACS-Jの2つの下位項目で明らかになった：言語記憶では右側頭皮質で，語流暢性では右前頭前皮質で，それぞれ正の相関を認めた。また，NEARは陰性症状を改善しなかったが，実施前後のPANSS陰性尺度の変化とNEAR開始前の2-back課題関連の［oxy-Hb］活性化の程度が右前頭皮質で負の相関を示し，ベースラインでの作業記憶課題で生じる脳血液量変化がNEARの陰性症状の効果予測因子となる可能性が示唆された。

統合失調症でみられる，作業記憶課題でのhypofrontality[4]はtrait markerと考えられた時期もあった。しかし，近年の神経機能画像研究の結果，集中的な認知リハビリテーションが作業記憶に関連する脳領域の活動性を高めることが明らかになり[2, 16]，統合失調症の病態であっても機能が可変的であること，心理社会的治療法が生物学的効果を発揮しうることが注目されている。本研究の結果でも，NEARは2-back課題に関するトレーニングを含まないが，6ヵ月間の実践によって，この課題に関連する皮質領域の機能的可塑性を起こすポテンシャルを有することが示唆された。本研究の対象集団では，BACS-Jの作業記憶は改善しなかったが，より多数の集団では，通常のリハビリテーションを受けた対照群に比べて有意な改善効果が認められており[8]，［oxy-Hb］活性化を指標とする脳機能の改善が認知機能の改善を媒介している可能性が高い。実際，言語記憶，語流暢性では，NEARによる認知機能の改善度と［oxy-Hb］活性化量の増加程度が，一部の皮質領域で正の相関を示すことはこの可能性を支持する。正常対照群では2-back課題に伴うfMRIを一定期間おいて反復施行すると，行動指標は変化しないが，学習効果や新規性の低下のために関連皮質の活性化程度が減弱することが知られており[16]，NEAR施行後の脳機能の活性化はNEARの生物学的効果と考えられる。

また，NEARで作業記憶関連の機能変化が生じる脳領域は，前述の通り，左右背外側前頭前野（BA 9，46），左腹外側前頭前野（BA 44および45，Broca野），左右前頭極部（BA 10）であった。これらの皮質領域は，Cohenらの研究[5]やOwenらのメタ解析[13]で明らかになった，健常者にみられるn-back課題の活性化領域に含まれている[5, 13]。本研究は予備的検討の段階にあり，しかもNIRSでは内側

前頭皮質，後部皮質，皮質下核の機能変化を評価できないが，今回得られた活性化領域の分布パターンから，NEARがもたらす脳機能の改善効果は，健常者で活性化される領域の“ノーマリゼーション”の方向への変化であり，健常者で活性化されない領域に生じた代償的変化ではない可能性が示唆される。

NEAR以外にも多様な手法の認知矯正療法が存在する[11]が，認知課題関連の脳血流量変化を指標とする脳機能の改善を介して認知機能が改善を示す点は共通している[2, 14, 16]。特に，Subramaniamらは，聴覚および視覚に関する識別能力，表情からの感情認知を中心とする社会認知機能を標的とする系統的アプローチによって“reality monitoring”課題の成績が向上することを示した[14]。この課題は，モニターに提示された単語について，自他のいずれが予め挙げたものかを区別するもので，統合失調症では自身が挙げた単語の識別が不良とされる。この課題の行動指標と相関する内側前頭前皮質の活性化の変化が大きいほど，リハビリテーション修了後6ヵ月で評価した社会機能が良好であり，この課題の改善度は社会機能に対するリハビリテーションの効果予測因子となりうる[14]。また，Eackらも，神経認知と社会認知の両障害を標的とする2年間のcognitive enhancement therapyが，左の海馬，海馬傍回，紡錘状回，扁桃体の体積減少を軽減し，何らかの神経保護作用をもつことを明らかにした[6]。認知矯正療法によって脳機能が改善するメカニズムにはまだほとんど手がつけられていないが，関連する神経回路の可塑性に加えて，Eackらが提唱する神経保護作用が関係する可能性が考えられる。

本研究の限界点は，①対照群（デイケア等に定期的に通所し，治療者との接触時間を統制した患者群と健常対照群）との比較がない，②RCTでない，③NIRSを用いたため，脳機能の変化を検出できない脳領域（内側前頭前皮質，頭頂葉等の後部皮質，皮質下核）がある，④NIRSの計測値には皮膚血流が含まれる可能性がある，⑤多重検定の影響を考慮に入れていない，という点である。今後はこれらの点を改善するとともに，fMRIの導入によって，より信頼性の高い結果を提示することが必要である。

文　献

1）Bilder RM, Goldman RS, Robinson D, et al（2000）Neuropsychology of first-episode schizophrenia：Initial characterization and clinical correlates. Am J Psychiatry, 157：549-559.

2）Bor J, Brunelin J, d'Amato T, et al（2011）How can cognitive remediation therapy modulate brain activations in schizophrenia? An fMRI study. Psychiatry Res, 192：160-166.

3）Bratti IM and Bilder RM（2006）Neurocognitive deficits and first-episode schizophrenia. In：The early course of schizophrenia.（eds Sharma T. and Harvey PD）Oxford Pr, pp 87-110.

4）Callicott JH, Mattay VS, Bertlino A, et al（1999）Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex, 9：20-26.

5）Cohen JD, Perlstein WM, Braver TS, et al（1997）Temporal dynamics of brain activation during a working memory task. Nature, 386：604-608.

6）Eack SM, Hogarty GE, Cho RY, et al（2010）Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia. Arch Gen Psychiatry, 67：674-682.

7）Green MF, Kern RS and Heaton RK（2004）Longitudinal studies of cognition and functional outcome in schizophrenia：implications for MATRICS. Schizophr Res, 72：41-51.

8）Ikezawa S, Moagami T, Hayami Y, et al（2012）The pilot study of a Neuropsychological Educational Approach to Cognitive Remediation for patients with schizophrenia in Japan. Psychiatry Res, 195：107-110.

9）Kaneda Y, Sumiyoshi T, Keefe R, et al（2007）Brief assessment of cognition in schizophrenia：validation of the Japanese version. Psychiatry Clin Neurosci, 61：602-609.

10）Kay SR, Fiszbein A and Opler LA（1987）The positive and negative syndrome scale（PANSS）for schizophrenia. Schizophr Bull, 13：261-276.

11）McGurk SR, Twamley EW, Sitzer DI, et al（2007）A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry, 164：1791-1802.

12）Medalia A and Choi J（2009）Cognitive remediation in schizophrenia. Neuropsychol Rev, 19：353-364.

13）Owen AM, McMillan KM, Laird AR, et al（2005）N-back working memory paradigm：a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25：46-59.

14）Subramaniam K, Luks TL, Fisher M, et al（2012）Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. Neuron, 73：842-853.

15) Takizawa R, Kasai K, Kawakubo Y, et al (2008) Reduced frontopolar activation during verbal fluency task in schizophrenia : a multi-channel near-infrared spectroscopy study. Schizophr Res, 99 : 250-262.

16) Wykes T, Brammer M, Mellers J, et al (2001) Effects on the brain of a psychological treatment : cognitive remediation therapy : functional magnetic resonance imaging in schizophrenia. Br J Psychiatry, 181 : 144-152.

■ ABSTRACT

Preliminary study on the effects of cognitive remediation on the hemodynamic responses in the frontal and temporal cortices of patients with schizophrenia : multi-channel near-infrared spectroscopy study

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We conducted a preliminary study to investigate the effects of a Neuropsychological Educational Approach to Cognitive Remediation (NEAR), one of the cognitive remediation therapies, on neurocognitive functions assessed by Japanese version of Brief Assessment of Cognition in Schizophrenia (BACS-J), and on prefrontal and temporal hemodynamic responses during working memory (WM) task (2-back, letter version) using 52-channel near-infrared spectroscopy (NIRS). We assessed sixteen patients with schizophrenia or schizoaffective disorder twice with an interval of six months. As previously reported, after NEAR, they showed significant improvement in four subcomponents of BACS-J, that is, verbal memory, motor speed, attention, executive functions along with composite score representing overall neurocognitive function. After NEAR, the patient group showed a significant increase in brain activation in bilateral cortical regions associated with working memory. In addition, the amount of enhancement in some cognitive subcomponents was positively correlated with the magnitude of an increase in hemodynamic response during WM task predominantly in right hemispheres. These findings suggest that neurocognitive deficits in schizophrenia and its related disorder, and their underlying neural dysfunction can be improved by NEAR.

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Research Article

Evaluation of Factors Affecting Continuous Performance Test Identical Pairs Version Score of Schizophrenic Patients in a Japanese Clinical Sample

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Aim. Cognitive impairment in schizophrenia strongly relates to social outcome and is a good candidate for endophenotypes. When we accurately measure drug efficacy or effects of genes or variants relevant to schizophrenia on cognitive impairment, clinical factors that can affect scores on cognitive tests, such as age and severity of symptoms, should be considered. To elucidate the effect of clinical factors, we conducted multiple regression analysis using scores of the Continuous Performance Test Identical Pairs Version (CPT-IP), which is often used to measure attention/vigilance in schizophrenia. *Methods.* We conducted the CPT-IP (4-4 digit) and examined clinical information (sex, age, education years, onset age, duration of illness, chlorpromazine-equivalent dose, and Positive and Negative Symptom Scale (PANSS) scores) in 126 schizophrenia patients in Japanese population. Multiple regression analysis was used to evaluate the effect of clinical factors. *Results.* Age, chlorpromazine-equivalent dose, and PANSS-negative symptom score were associated with mean d′ score in patients. These three clinical factors explained about 28% of the variance in mean d′ score. *Conclusions.* As conclusion, CPT-IP score in schizophrenia patients is influenced by age, chlorpromazine-equivalent dose and PANSS negative symptom score.

1. Introduction

Schizophrenia is a complex, heritable psychiatric disorder, affecting approximately 1% of the general population. The heritability of schizophrenia is estimated to be 64% [1]. Genes relevant to schizophrenia or variants that may modulate risk for the disease have been identified using both linkage and candidate-based or whole-genome association studies [2–5]. A complementary approach examines the genetics of schizophrenia from the neurobiological perspective with neurocognitive endophenotypic markers of putative brain function. The underlying brain dysfunctions (and related endophenotypes) are more stable, trait-like markers that can be used to refine the psychiatric diagnosis. This approach is further motivated by the need to elucidate pathophysiological pathways after candidate variants are established [6].

The Consortium on the Genetics of Schizophrenia is a 7-site collaboration that examines the genetic architecture of quantitative endophenotypes in families with schizophrenia. The authors suggested that the Continuous Performance Test Identical Pairs Version (CPT-IP), Degraded Stimulus Continuous Performance Test (DS-CPT), Verbal Declarative Memory Test, Working Memory Test, and Penn Computerized Neurocognitive Battery are the most appropriate tests to evaluate endophenotypes relevant to schizophrenia. Furthermore, the heritability of attention/vigilance using sample comprised of 30 healthy families was estimated to be 0.39 and 0.49 based on verbal and spatial CPT-IP scores, respectively

[7]. The effect size was 1.18 when schizophrenia patients and controls were compared. Accordingly, the comparison between the first-degree relatives of schizophrenic patients and controls resulted in smaller effect size (0.54) [6].

CPT-IP is included as a core test in major psychological batteries used to evaluate cognitive functioning of psychiatric patients, such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia and the Consensus Cognitive Battery (MCCB) for schizophrenia. Cognitive impairment is one of the core symptoms of schizophrenia and is associated with impaired quality of life and poor outcome [8–10]. The CPT-IP test used to evaluate one of the cognitive endophenotypes related to schizophrenia. Specifically, CPT-IP can measure the attention/vigilance deficit that is commonly found in schizophrenic subjects and those who are at risk for the disorder [11].

Biological phenotypes (e.g., cognitive or central executive functions) are thought to more closely reflect the effects of genetic variation compared with manifested psychiatric illness; therefore, endophenotype studies have proven to be more robust and require smaller sample sizes than purely diagnosis-based studies. When genetic effects on cognitive performance are evaluated, it is important to consider measurement errors [12] as well as the effect of clinical factors that may strongly affect CPT-IP scores. In that regard, except for several reports that have evaluated the association between age and Positive and Negative Symptom Scale (PANSS) scores on cognitive performance [13], there are no comprehensive studies that looked for relevant covariates that may influence CPT-IP scores. We conducted an analysis of factors that can affect CPT-IP scores (e.g., sex, age, education years, onset age, duration of illness, chlorpromazine equivalent dose, and PANSS scores) using a Japanese population-based sample.

2. Methods

2.1. Participants. This study was approved by the Ethics Committee of each participating institute, and written informed consent was obtained from each participant. Patients were included in the study if they (1) met DSM-IV criteria for schizophrenia, (2) were physically healthy, and (3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or known mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with patients and families and review of medical records. The rate of the samples excluded due to a lack of consensus was less than 5%. All subjects were unrelated to each other, living in the central area of the mainland of Japan, and self-identified as Japanese. The study included 126 unrelated Japanese patients with schizophrenia (mean age, 44.4 ± 13.3 years; 80 males and 46 females).

2.2. Measurement Settings. There are a variety of CPTs, the more commonly used being CPT-X/AX, DS-CPT, and CPT-IP [11]. CPT-IP has evolved over the course of the New York High-Risk Project [14]. In CPT-IP, the target is defined as the second stimulus in any pair of identical stimuli. The benefit of using CPT-IP instead of the other tests is due to the structure and simplicity of the examination. In other words, no number or number sequence is specified, as in the X/AX design, and the subject does not need to memorize each stimulus presented as in the DS-CPT, which can increase the information-processing load. We used CPT-IP program Release 4.0 (NewCPT.exe, Copyright 1982–2004 by Barbara A. Cornblatt, All Rights Reserved). The PC monitor was 10.4′ and letter size was at least 2.2 × 1.5 cm [7]. The distance between the subjects and the monitor was at least 50 cm.

Stimuli were flashed on the screen at a constant rate of 1 per set, with a stimulus "on" time of 50 msec and a stimulus "off" time of 950 msec. Stimuli were four-digit numbers and were presented 150 times. In each 150 trial conditions, 30 of the trials (20%) were target trials and required a response. Target trials were those on which the second of a pair of two identical stimuli appeared. Responses to target trials were scored as hits [7]. Condition also included a number of catch trials on which the stimulus presented was similar but not identical to that of the preceding trial. Responses to catch trials were considered a specific type of commission error, referred to as false alarms. There were 30 catch trials (20%) in our test. The remaining trials in both conditions were 90 randomly distributed fillers. Responses to filler trials, referred to as random errors, were also considered to be commission errors but were analysed independently of false alarms. We conducted the four-digit CPT-IP two times, with a resting time between the two examinations of 1 min. Mean d′ score was defined as the mean of first and second d′ score.

2.3. Clinical Factors. Chlorpromazine (CPZ) equivalent dose was calculated according to standard methodology based on a Japanese clinical sample [15, 16]. The PANSS was used to evaluate the severity of symptoms in patients [17].

2.4. Statistical Analysis. IBM SPSS Statistics Version 19 was used for all analyses. Intraclass correlation coefficient was calculated in d′, hits, false alarm, and random errors. Multiple regression was performed for the analysis of mean of d′ score using clinical information (sex, age, education years, onset age, duration of illness, CPZ equivalent dose of antipsychotics, and PANSS score) (positive, negative and general psychopathology). Multiple regression models were analysed using forward-backward stepwise selection. Multiple correlation coefficient adjusted for the degree of freedom (R_a^2), analysis of variance (ANOVA) P-value, and Durbin-Watson ratio were calculated to evaluate the extent of model fitting. The significance level was set at $P = 0.05$.

3. Results

Clinical profile of participants is shown in Table 1. The intraclass correlation coefficient (ICC) of the mean d′ score was 0.71 (Table 2). In multiple regression analysis, age, CPZ equivalent dose, and PANSS-negative symptom score were significantly associated with mean d′ score (Table 3). Durbin-Watson ratio indicated the absence of spurious

Table 1: Participants profile.

	Patients (n = 126)	
Sex		
Male	80	
Female	46	
	Mean	SD[a]
Age (y)	44.4	13.3
Education years (y)	12.4	2.4
Onset age (y)	26.7	10.0
Duration of illness (y)	17.6	13.0
Chlorpromazine equivalent dose (mg/day)	631.9	434.0
PANSS score		
Positive (7–49)	16.3	5.2
Negative (7–49)	19.0	5.5
General psychopathology (16–112)	36.2	9.3
Total (30–210)	71.6	17.7
Clinical diagnosis		
Paranoid type	46	
Disorganized type	3	
Catatonic type	1	
Residual type	65	
Unknown	11	
Polytherapy		
Antipsychotics		
Monotherapy	26	
Risperidone	62	
Olanzapine	16	
Aripiprazole	17	
Other atypical drug	3	
Typical drug	2	

[a]standard deviation.

Table 2: Measurement results of 4-digit CPT-IP.

P	Patients (n = 126)		
	Mean	SD[a]	ICC[b]
d′			
1st	1.29	0.84	0.71
2nd	1.55	0.96	
mean	1.42	0.84	
Hits (0–30)			
1st	18.4	7.2	0.77
2nd	19.6	6.9	
False alarms (0–30)			
1st	6.3	4.6	0.70
2nd	5.7	4.7	
Random errors (0–90)			
1st	4.8	8.9	0.53
2nd	3.5	4.9	

[a]standard deviation
[b]intraclass correlation coefficient.

regression. Although no strong correlation (>0.8) was observed in all clinical parameters, the Pearson's correlation between age and duration of illness was high (0.72).

4. Discussion

CPT-IP is a major neurocognitive examination used to assess cognitive impairment among psychiatric patients. Included as a subtest in the MCCB, CPT-IP scores are often used to assess drug efficacy in clinical trials or endophenotypes in genetic studies. Confounding factors, such as measurement error or influence of clinical data, can hamper interpretation of results. Thus, to elucidate the effects of clinical data (age, sex, education years, duration of illness, onset age, CPZ equivalent dose, and PANSS score) on CPT-IP score in schizophrenia patients, we performed a multiple regression analysis in Japanese people suffering from schizophrenia.

4.1. Main Findings. Age and PANSS-negative symptom score were statistically associated with mean d′ score in schizophrenia patients. This finding is in concordance with a previous study [18]. Additionally, our results suggest that CPZ-equivalent dose affects CPT-IP score. Overall, using a relatively large Japanese clinical sample of schizophrenia, we showed that age, CPZ-equivalent, dose and PANSS-negative symptom score can have a major effect on the CPT-IP scores and therefore should be taken into the account when interpreting results obtained from patients with schizophrenia. Age, CPZ-equivalent dose, and PANSS negative symptom score explained about 28% of the variance in mean d′ score.

4.2. Limitations. There are several limitations that should be considered when interpreting the results of the present study. Multiple regression analysis findings in schizophrenia patients would benefit if we had been able to obtain more clinical information, such as IQ score and duration of untreated psychosis. As we could not find significant effects of sex, age at disease onset, duration of illness, and PANSS-positive and general psychopathology score in this study, weak effects of these factors might be observed when the sample size is increased.

5. Conclusion

We investigated how covariates (age, CPZ-equivalent dose, and PANSS-negative symptom score) affect mean d′ score of CPT-IP. This is the first study using a single independent large Japanese schizophrenia sample set, known as homogeneous in terms of genetic makeup. Our study suggested that those effects should be carefully considered especially when CPT-IP is performed to detect small effect size factors which are expected to be found in case of common risk variants associated with schizophrenia or cognitive-enhancing drugs. Thus, as CPT-IP is likely to be an endophenotypic measure in molecular genetic studies of schizophrenia in the post-genome-wide association study era [19, 20], our data show

Table 3: Multiple regression analysis of mean d′ score.

Multiple regression analysis						
Forward-backward stepwise selection						
Clinical factors	Patients (n = 126) Setting: P_{in} = 0.05, P_{out} = 0.1					
	PRC[a]	S-PRC[b]	VIF[c]	95% CI[d] Lower	95% CI[d] Upper	P value
Age (y)	−0.031	−0.45	1.04	−0.041	−0.020	**<0.001**
CPZ-equivalent dose (mg/day)	−0.00038	−0.21	1.01	−0.001	<0	**0.012**
PANSS-negative symptom score (7–49)	−0.026	−0.16	1.04	−0.052	<0	**0.017**
Intercept	3.54	—	—	2.89	4.19	<0.001
$\hat{R}^{2e}$			0.28			
ANOVA P value			**<0.001**			
Durbin-Watson ratio			1.93			

[a]partial regression coefficient
[b]standardized partial regression coefficient
[c]variance inflation factor
[d]confidence interval
[e]multiple correlation coefficient adjusted for the degrees of freedom.

that careful assessment of confounding factors is essential for interpretation of findings.

Authors' Contribution

T. Koide and B. Aleksic contributed equally to this work.

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References

[1] P. Lichtenstein, B. H. Yip, C. Björk et al., "Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study," *The Lancet*, vol. 373, no. 9659, pp. 234–239, 2009.

[2] H. Stefansson, R. A. Ophoff, S. Steinberg et al., "Common variants conferring risk of schizophrenia," *Nature*, vol. 460, no. 7256, pp. 744–747, 2009.

[3] J. Shi, D. F. Levinson, J. Duan et al., "Common variants on chromosome 6p22.1 are associated with schizophrenia," *Nature*, vol. 460, no. 7256, pp. 753–757, 2009.

[4] S. M. Purcell, N. R. Wray, J. L. Stone et al., "Common polygenic variation contributes to risk of schizophrenia and bipolar disorder," *Nature*, vol. 460, no. 7256, pp. 748–752, 2009.

[5] M. Y. M. Ng, D. F. Levinson, S. V. Faraone et al., "Meta-analysis of 32 genome-wide linkage studies of schizophrenia," *Molecular Psychiatry*, vol. 14, no. 8, pp. 774–785, 2009.

[6] R. E. Gur, M. E. Calkins, R. C. Gur et al., "The consortium on the genetics of schizophrenia: neurocognitive endophenotypes," *Schizophrenia Bulletin*, vol. 33, no. 1, pp. 49–68, 2007.

[7] B. A. Cornblatt, N. J. Risch, G. Faris, D. Friedman, and L. Erlenmeyer-Kimling, "The continuous performance test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families," *Psychiatry Research*, vol. 26, no. 2, pp. 223–238, 1988.

[8] M. F. Green, "What are the functional consequences of neurocognitive deficits in schizophrenia?" *American Journal of Psychiatry*, vol. 153, no. 3, pp. 321–330, 1996.

[9] M. F. Green, R. S. Kern, D. L. Braff, and J. Mintz, "Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"?" *Schizophrenia Bulletin*, vol. 26, no. 1, pp. 119–136, 2000.

[10] M. F. Green, R. S. Kern, and R. K. Heaton, "Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS," *Schizophrenia Research*, vol. 72, no. 1, pp. 41–51, 2004.

[11] B. A. Cornblatt and J. G. Keilp, "Impaired attention, genetics, and the pathophysiology of schizophrenia," *Schizophrenia Bulletin*, vol. 20, no. 1, pp. 31–46, 1994.

[12] K. S. Kendler and M. C. Neale, "Endophenotype: a conceptual analysis," *Molecular Psychiatry*, vol. 15, no. 8, pp. 789–797, 2010.

[13] K. H. Nuechterlein, M. F. Green, R. S. Kern et al., "The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity," *American Journal of Psychiatry*, vol. 165, no. 2, pp. 203–213, 2008.

[14] L. Erlenmeyer-Kimling and B. A. Cornblatt, "A summary of attentional findings in the New York high-risk project," *Journal of Psychiatric Research*, vol. 26, no. 4, pp. 405–426, 1992.

[15] A. Inagaki and T. Inada, "Dose equivalence of psychotropic drugs. Part XX: dose equivalence of novel antipsychotics: blonanserin," *Japanese Journal of Clinical Psychopharmacology*, vol. 11, pp. 887–890, 2008.

[16] A. Inagaki and T. Inada, "Dose equivalence of psychotropic drugs. Part XXII: dose equivalence of depot antipsychotics III: risperidon long-acting injection," *Japanese Journal of Clinical Psychopharmacology*, vol. 13, pp. 1349–4353, 2010.

[17] S. R. Kay, A. Fiszbein, and L. A. Opler, "The positive and negative syndrome scale (PANSS) for schizophrenia," *Schizophrenia Bulletin*, vol. 13, no. 2, pp. 261–276, 1987.

[18] M. R. Nieuwenstein, A. Aleman, and E. H.F. De Haan, "Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: a meta-analysis of WCST and CPT studies," *Journal of Psychiatric Research*, vol. 35, no. 2, pp. 119–125, 2001.

[19] K. E. Burdick, P. DeRosse, J. M. Kane, T. Lencz, and A. K. Malhotra, "Association of genetic variation in the MET proto-oncogene with schizophrenia and general cognitive ability," *American Journal of Psychiatry*, vol. 167, no. 4, pp. 436–443, 2010.

[20] T. D. Cannon, "Candidate gene studies in the GWAS era: the MET proto-oncogene, neurocognition, and schizophrenia," *American Journal of Psychiatry*, vol. 167, no. 4, pp. 369–372, 2010.

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Sexual dysfunction and hyperprolactinemia in Japanese schizophrenic patients taking antipsychotics

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ABSTRACT

This study aimed to estimate the prevalence of sexual dysfunction, evaluated by the Nagoya Sexual Function Questionnaire (NSFQ), and hyperprolactinemia in patients with schizophrenia and examine a relationship between sexual dysfunction and serum prolactin levels. This cross-sectional, comparative study was performed using a sample comprising 195 Japanese schizophrenic in- and outpatients treated with antipsychotics (117 males and 78 females). Data were collected from October 2009 to January 2010 using single, cross-sectional ratings of sexual function assessed by the NSFQ and concurrent measurement of serum prolactin levels. The prevalence of sexual dysfunction in patients with schizophrenia was high (males 66.7%; females 79.5%). Hyperprolactinemia (>25 ng/ml) was highly prevalent among schizophrenia patients, affecting 53.8% of females and 51.3% of males. Among female patients, 16.7% had prolactin levels>100 ng/ml. There was no relationship between sexual dysfunction and serum prolactin levels. The present study demonstrated a higher prevalence of sexual dysfunction and hyperprolactinemia in Japanese schizophrenia patients. Clinicians should keep these problems in mind and discuss potential solutions with patients to improve patients' quality of life and adherence to therapy.

1. Introduction

Despite evidence showing that sexual dysfunction is common in patients with schizophrenia (Cutler, 2003; Ghadirian et al., 1982; Kotin et al., 1976; Smith et al., 2002), physicians tend to overlook or disregard sexual dysfunction during the psychiatric evaluation of schizophrenic patients. For example, approximately 50–70% of male schizophrenic patients and 30–50% of female schizophrenic patients have sexual dysfunction (Fakhoury et al., 2001; Ghadirian et al., 1982). Sexual disturbances in such patients may be due to various factors, including the symptoms of schizophrenia (Aizenberg et al., 1995), secondary effects of living with a severe, chronic mental health condition, or adverse effects of antipsychotics or other medications (Smith et al., 2002). In particular, drugs that raise prolactin levels, such as risperidone, are associated with significantly higher rates of sexual problems (40–60%) compared with prolactin-sparing drugs (e.g., quetiapine, ziprasidone, and aripiprazol) (<30%) (Knegtering et al., 2004; Knegtering et al., 2006; Montejo Gonzalez et al., 2005; Montejo and Rico-Villademoros, 2008a; Montejo et al., 2010a, 2010b; Serretti and Chiesa, 2011).

The studies mentioned above present data about sexual dysfunction among patients with schizophrenia in Western countries. Conversely, there are few studies in Asian populations, including Japanese patients (Fujii et al., 2010). The prevalence of sexual concerns differs in healthy individuals according to their ethnicity. However, the accurate estimation of prevalence is complicated by the reluctance of psychiatric staff (i.e., psychiatrists and nurses) to discuss sexual concerns with patients (Withersty, 1976; Wolfe and Menninger, 1973). These problems are more pronounced in Far Eastern countries, perhaps due to socio-cultural reasons (Moreira et al., 2005, 2006). From a clinical point of view, it is important to be aware of sexual dysfunction in patients with schizophrenia and apply the knowledge of sexual dysfunction to the treatment of schizophrenia, because this symptomatology is relatively common among patients and may contribute to poor quality of life (QOL) and poor adherence with therapy (Gopalakrishnan et al., 2006; Olfson et al., 2005).

In Western countries, several instruments are used to assess sexual dysfunction, including the Arizona Sexual Experience Scale (ASEX)

Abbreviations: ASEX, Arizona Sexual Experience Scale; CLIA, chemiluminescence immunoassay; CP, chlorpromazine; CSFQ, Changes in Sexual Functioning Questionnaire; NSFQ, Nagoya Sexual Function Questionnaire; PRSexDQ-SALSEX, Psychometric Properties of the Psychotropic-Related Sexual Dysfunction Questionnaire; QOL, Quality Of Life; UKU, Udvalg for Kliniske Undersogekser Side Effect Rating Scale.

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(McGahuey et al., 2000), the sexual part of Udvalg for Kliniske Undersogekser Side Effect Rating Scale (UKU) (Lingjaerde et al., 1987), Psychometric Properties of the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX) (Montejo and Rico-Villademoros, 2008b; Montejo et al., 2000), and the Changes in Sexual Functioning questionnaire (CSFQ) (Clayton et al., 1997). Although most instruments are useful (in particular, SALSEX is very brief, user-friendly, and reliable), some of them are rather long (CSFQ has 36 items for men and 35 items for women). In addition, the contents of ASEX, UKU, and PRSexDQ-SALSEX include vaginal dryness, vaginal lubrication, and orgasmic dysfunction, which may be intrusive for *patients and clinicians who feel embarrassed to talk about sexual concerns directly (Asian people in particular)*, and difficult to use (UKU involves a semi-structured interview). Therefore, it may not be easy to use these instruments among schizophrenic patients who are reluctant to discuss their sexual concerns, a topic that is sometimes considered taboo not only in Asian but also in Western countries. To address this problem, we recently developed and validated a short, minimally intrusive, and self-administered instrument called the Nagoya Sexual Function Questionnaire (NSFQ) (Kikuchi, et al., 2011).

From a pharmacological point of view, side effects of antipsychotics characterized by sexual dysfunction are related to hyperprolactinemia (Haddad and Wieck, 2004). More than 50% of schizophrenic patients treated with a prolactin-raising antipsychotic drugs experience hyperprolactinemia (Haddad and Wieck, 2004). Psychiatric staff tend to disregard symptoms of hyperprolactinemia that involve sexual dysfunction (loss of/decreased libido, erectile dysfunction [men], gynecomastia [men], amenorrhoea/oligomenorrhoea [women]), because clinical signs are subtle or even if the symptoms of hyperprolactinemia become obvious, patients and professionals are embarrassed to discuss them (Haddad and Wieck, 2004). Moreover, it is unclear to what extent sexual dysfunction is due to a direct effect of increased prolactin levels (Haddad and Wieck, 2004). Additionally, sexual dysfunction in Asian schizophrenic patients is a topic that has not been fully investigated due to the socio-cultural reasons stated above.

Considering the lack of the studies conducted in a Japanese population, and the implication for therapeutic intervention, our study aimed to estimate the prevalence of sexual dysfunction obtained from the measurement of NSFQ and hyperprolactinemia in Japanese schizophrenic patients and examine the relationship between sexual dysfunction and serum prolactin levels.

2. Methods

The present study was a cross-sectional, comparative trial. Data were collected from October 2009 to January 2010 using a single, cross-sectional rating of sexual function assessed by the NSFQ. Concurrently, measurement of serum prolactin levels was performed. Subjects were returning outpatients and inpatients with a diagnosis of schizophrenic disorder according to DSM-IV criteria. All patients had been stabilized on antipsychotic medication for more than 8 weeks. Patients were excluded if they had a general medical condition or a history of a surgical procedure known to cause sexual dysfunction. Psychotropic medications such as benzodiazepines, anticholinergics, antidepressants, and mood stabilizers were allowed if the patients were already receiving these medications prior to study enrollment. However, in this research, no patient was receiving antidepressants.

After obtaining demographic and medication/treatment information, an introductory presentation was made, during which the nature of the study was explained to the patients, and written informed consent was obtained from patients willing to participate. The study was approved by the Ethics Committee of the Nagoya University School of Medicine.

The NSFQ is a self-administered sexual function scale (Kikuchi, et al., 2011). The NSFQ was developed through the collaborative effort of specialists in psychiatry and urology. The NSFQ consists of seven items. Each item is evaluated on a six-point scale: (1) not at all; (2) almost never; (3) sometimes; (4) often; (5) always; and (6) unsure. The answers of (1) through (5) are assigned scores of 1 to 5 points, respectively, and (6) is assigned 1 point; total scores range from 5 to 35. The items for men are: 1) pulsating sensation in the breast/mammary area; 2) galactorrhea; 3) interest in women; 4) sexual interest; 5) sexual self-confidence; 6) erectile dysfunction; and 7) ejaculatory dysfunction. The items for women are: 1) menstrual irregularity; 2) pulsating sensation in the breast/mammary area; 3) galactorrhea; 4) interest in men; 5) sexual interest; 6) sexual self-confidence; and 7) sexual arousal. Subjects were asked to answer questions 6 and 7 if they gave scores of (2)–(5) for questions 1–5. To estimate the potential prevalence of sexual dysfunction, subjects with a score of 3 or higher on any relevant items in the NSFQ were considered to have sexual side effects. Subjects with a score of 3, 4, or 5 on each of the relevant items were considered to have mild, moderate, or severe sexual side effects, respectively. The prevalence of total sexual dysfunction was calculated by the following equation: the number of patients with a score of 3 or higher on any of the NSFQ items was divided by the total number of patients regardless of sexual dysfunction. Data for menstrual irregularity were recorded only for female subjects younger than 45 years. Prolactin levels were determined by chemiluminescence immunoassay (CLIA) (Siemens, Munich, Bayern, Germany). Blood was drawn for prolactin levels from 9:30 a.m. to 10:30 a.m. In this study, normal prolactin levels for female and male patients were $\leq$25 ng/ml and $\leq$20 ng/ml, respectively. All analyses were performed using JMP version 5.1.2 (SAS Institute, Inc., Cary, NC). The student *t*-test was used to compare: (1) mean prolactin levels between patients with and without sexual dysfunction, and (2) mean total score of the NSFQ and prolactin levels between men and women. We performed one-way factorial analysis of variance and multiple comparison tests (Tukey's Honestly Significant Difference test) to compare mean total NSFQ scores of among stratified prolactin levels (male: 0–20 ng/ml, 20–50 ng/ml, 50–100 ng/ml, female: 0–25 ng/ml, 25–50 ng/ml, 50–100 ng/ml, 100–150 ng/ml, 150–200 ng/ml), and mean total NSFQ scores and prolactin levels among groups receiving aripiprazole, olanzapine, risperidone, and polytherapy. The chi square test was used to test for differences between the frequency of total sexual dysfunction between men and women, and among groups receiving aripiprazole, olanzapine, risperidone, and polytherapy in men and women. We performed multiple regression analysis with the total NSFQ score as the dependent variable and prolactin level, age, sex, duration of illness, duration of treatment, number of antipsychotics, and dose of antipsychotics (chlorpromazine [CP] equivalent) as independent variables. A p value$<$0.05 was considered statistically significant.

3. Results

3.1. Characteristic of patients

Clinically relevant patient characteristics are presented in Table 1. Patients were divided into monotherapy groups receiving a single antipsychotic of risperidone, olanzapine, aripiprazole, or others, and the polytherapy group. The mean CP equivalent doses of antipsychotics and concomitant drugs (benzodiazepines and anticholinergics) in each group are shown in Table 1.

3.2. Prevalence of sexual dysfunction

Prevalence of sexual dysfunction is shown in Table 2. We observed gender-specific differences in the prevalence of sexual dysfunction. Specifically, the prevalence of moderate and severe sexual dysfunction in female patients was significantly higher than in male patients (chi square 6.633 p = 0.01).

Table 1
Characteristic of patients.

	Males	Females
N	117	78
Age (years)	43.9 ± 12.7	45.9 ± 12.1
Duration of illness (months)	247.2 ± 194.0	231.5 ± 162.9
Treatment of illness (months)	226.5 ± 187.2	199.9 ± 164.2
Dose of antipsychotics (mg/day)[a]	629.7 ± 406.7	595.4 ± 379.5
Dose of concomitant benzodiazepines (mg/day)[b]	7.0 ± 11.8	1.0 ± 1.9
Dose of concomitant anticholinergics (mg/day)[c]	1.2 ± 1.7	0.6 ± 1.8
Drug group		
Risperidone only		
N	42	27
Dose of risperidone (mg/day)[a]	539.5 ± 288.4	570 ± 349.5
Dose of concomitant benzodiazepines (mg/day)[b]	1.6 ± 3.1	1.6 ± 2.2
Dose of concomitant anticholinergics (mg/day)[c]	1.6 ± 1.8	0.7 ± 2.1
Olanzapine only		
N	15	9
Dose of olanzapine (mg/day)[a]	507.1 ± 233.5	722.2 ± 120.1
Dose of concomitant benzodiazepines (mg/day)[b]	3.3 ± 4.7	0.8 ± 2.1
Dose of concomitant anticholinergics (mg/day)[c]	0.2 ± 0.8	0
Aripiprazole only		
N	14	17
Dose of aripiprazole (mg/day)[a]	344.6 ± 297.8	411.8 ± 228.1
Dose of concomitant benzodiazepines (mg/day)[b]	8.6 ± 17.8	0.5 ± 1.0
Dose of concomitant anticholinergics (mg/day)[c]	0	0.4 ± 1.2
Other drugs (as monotherapy)		
N	3	7
Dose of antipsychotics (mg/day)[a]	165.5 ± 92.6	218.5 ± 107.6
Dose of concomitant benzodiazepines (mg/day)[b]	3.4 ± 4.7	0
Dose of concomitant anticholinergics (mg/day)[c]	0	3.1 ± 4.4
Polytherapy		
N	45	18
Numbers of antipsychotics	2.5 ± 0.7	2.44 ± 0.8
Dose of antipsychotics (mg/day)[a]	878.1 ± 464.9	889.4 ± 461.0
Dose of concomitant benzodiazepines (mg/day)[b]	9.1 ± 11.1	1.0 ± 1.0
Dose of concomitant anticholinergics (mg/day)[c]	0.21 ± 0.8	0

Values are mean ± SD unless otherwise noted.
[a] Chlorpromazine-equivalent dose.
[b] Diazepam-equivalent dose.
[c] Biperiden-equivalent dose.

The most prevalent symptom of male sexual dysfunction was lack of sexual self-confidence in both the moderate and severe groups, whereas the most prevalent symptom of female sexual dysfunction was menstrual irregularity in the moderate group and lack of sexual interest in the severe group.

3.3. Total NSFQ score and serum concentrations of prolactin

The total NSFQ score and serum concentrations of prolactin are shown in Table 3. Results showed that hyperprolactinemia was highly prevalent among schizophrenia patients (males, 51.3%; females, 53.8%). Moreover, 16.7% of female patients showed extremely high concentrations of prolactin (>100 ng/ml). The mean prolactin level in female patients (45.3 ± 46.7 ng/ml) was significantly higher than in male patients (21.5 ± 16.7 ng/ml) ($t = 5.0357$, $p < 0.001$), but there was no significant difference between male patients (12.7 ± 5.5) and female patients (14.0 ± 5.1) in mean total NSFQ score ($t = 1.6743$, $p = 0.0957$). There were no significant differences in total NSFQ score among stratified prolactin levels in male patients ($F = 1.219$ $df = 116$, $p = 0.299$) and female patients ($F = 0.486$, $df = 77$, $p = 0.746$). Similar values of total NSFQ scores were observed in all stratified levels of prolactin.

3.4. Antipsychotic effect

Total NSFQ score, the frequency of total sexual dysfunction, and prolactin level of each antipsychotic treatment group are summarized by gender in Table 4. There were significant differences in the prolactin levels among the antipsychotic groups receiving aripiprazole, olanzapine, polytherapy, and risperidone in males ($F = 13.251$, $df = 114$, $p < 0.001$; aripiprazole < polytherapy, $p < 0.001$; aripiprazole < risperidone, $p < 0.001$; olanzapine < polytherapy, $p = 0.026$; olanzapine < risperidone, $p < 0.001$) and females ($F = 14.107$, $df = 70$, $p < 0.001$; aripiprazole < polytherapy, $p < 0.01$; aripiprazole < risperidone, $p < 0.001$; olanzapine < risperidone, $p < 0.01$). As a whole, prolactin levels became higher in the following order: aripiprazole, olanzapine, polytherapy, and risperidone. However, the total NSFQ scores were not significantly different among the groups receiving aripiprazole, olanzapine polytherapy, and risperidone in males ($F = 0.075$, $df = 114$, $p = 0.973$) and females ($F = 1.537$, $df = 70$, $p = 0.213$). There was no significant difference in the frequency of total sexual dysfunction among groups receiving aripiprazole, olanzapine polytherapy, and risperidone (males, from mild to severe, chi square 1.5508 $p = 0.82$; moderate and severe, chi square 4.3366 $p = 0.36$; females, from mild to severe, chi square 9.0318 $p = 0.06$; moderate and severe, chi square 7.6454 $p = 0.11$). The frequency of total sexual dysfunction (from mild to severe) becomes higher in the following order: risperidone (64.3%), polytherapy (64.4%), olanzapine (66.7%), and aripiprazole (78.6%) in males, and olanzapine (55.6%), aripiprazole (82.4%), polytherapy (83.3%), and risperidone (92.6%) in females. Moderate and severe total sexual dysfunction becomes higher in the following order: polytherapy (33.3%), aripiprazole (35.7%), risperidone (45.2%), and olanzapine (53.3%) in males, and olanzapine (33.3%), aripiprazole (58.8%), risperidone (66.7%), and polytherapy (72.2%) in females.

3.5. Multiple regression analysis

We performed multiple regression analysis with total NSFQ score as the dependent variable and prolactin level, age, sex, duration of illness, duration of treatment, number of antipsychotics, and dose of antipsychotics (CP equivalent) as independent variables; however, no statistically significant correlations were found (R 0.2126, $p = 0.2698$). No significant differences in mean prolactin levels were observed between the group with and without sexual dysfunction in males (prolactin level: 22.0 ± 17.0 in the group with sexual dysfunction, 20.6 ± 16.1 in the group without sexual dysfunction, $t = 0.4245$, $p = 0.6720$) and females (prolactin level: 50.0 ± 48.0 in the group with sexual dysfunction, 27.1 ± 37.1 in the group without sexual dysfunction, $t = 1.7694$, $p = 0.0808$).

4. Discussion

This study surveyed sexual dysfunction using a self-administered sexual functional scale, the NSFQ, and showed that sexual dysfunction is highly prevalent among Japanese patients suffering from schizophrenia. Our study revealed that patients' sexual dysfunction extended over multiple domains that were evaluated by different items of the NSFQ.

According to previous studies (Cutler, 2003; Ghadirian et al., 1982), the rate of sexual dysfunction was reported to be lower in female patients with schizophrenia than males with schizophrenia. However, Fujii et al. (2010) reported that sexual dysfunction in males is similar to that in females, and their results were consistent with our findings. As Fujii et al. noted, this tendency could be influenced by menstrual irregularities that are classified as sexual dysfunction. However, if menstrual irregularities (48.6%) were excluded from our dataset, the prevalence of sexual dysfunction in females did not change significantly (from 79.5% to 70.5%). The reason for the difference between the current study and prior research is that NSFQ reveals not only symptoms of sexual dysfunction that are obvious, such as menstrual irregularities, but also symptoms of sexual dysfunction that women are reluctant to discuss and therefore can be easily overlooked by medical professionals.

Table 2
Prevalence of sexual dysfunction in males and females.

Gender	Category	≥3 (from mild to severe) n (%)	≤3 n (%)	≥4 (moderate and severe) n (%)	≥4 n (%)
Males	Total sexual dysfunction	78 (66.7)	39 (33.3)	47 (40.2)	70 (59.8)
	Pulsating sensation in the breast/mammary area	12 (10.3)	–	6 (5.1)	–
	Galactorrhea	2 (1.7)	–	0 (0)	–
	Interest in women	46 (39.3)	–	19 (16.2)	–
	Sexual interest	48 (41)	–	18 (15.4)	–
	Sexual self-confidence	53 (45.3)	–	25 (21.4)	–
	Erectile dysfunction	33 (28.2)	–	14 (12.0)	–
	Ejaculatory dysfunction	33 (28.2)	–	17 (14.5)	–
Females	Total sexual dysfunction	62 (79.5)	16 (20.5)	46 (59.0)	32 (41.0)
	Menstrual irregularity	17/35 (48.6)	–	7/35 (20)	–
	Pulsating sensation in the breast/mammary area	21 (26.9)	–	6 (7.7)	–
	Galactorrhea	6 (7.7)	–	3 (3.8)	–
	Interest in men	33 (42.3)	–	13 (16.7)	–
	Sexual interest	36 (46.2)	–	19 (24.4)	–
	Sexual self-confidence	26 (33.3)	–	13 (16.7)	–
	Sexual arousal	18 (23.1)	–	12 (15.4)	–

The prevalence of slight to severe and moderate to severe sexual dysfunction in females was significantly higher than that in males (mild and severe sexual dysfunction, chi square 3.900 $p = 0.0483$; moderate and severe sexual dysfunction, chi square 6.662 $p = 0.0098$).

Our results also showed that hyperprolactinemia was highly prevalent among schizophrenia patients, and mean prolactin levels were significantly higher in female patients than in male patients. In particular, 16.7% of female patients showed extremely high concentrations of prolactin (>100 ng/ml). Prior cross-sectional studies estimating the prevalence of hyperprolactinemia in schizophrenia patients treated with conventional antipsychotics or risperidone reported that approximately 60% of women and 40% of men had hyperprolactinemia (Haddad and Wieck, 2004; Halbreich, et al., 2003; Smith et al., 2002), with mean prolactin levels in women of 62.7 ng/ml and those in men of 32.4 ng/ml (Halbreich et al., 2003). Moreover, prior cross-sectional studies estimating the prevalence of hyperprolactinemia in schizophrenia patients treated with atypical antipsychotics (olanzapine, 29 patients; clozapine, 28 patients; risperidone, 19 patients) showed that 42% of women and 21% of men had hyperprolactinemia (Melkersson, 2005). In our study, many patients were treated with conventional antipsychotics or risperidone (men, 74.4%; women; 57.7%), so the results of this study were similar to previous studies in patients treated with conventional antipsychotics or risperidone.

Hyperprolactinemia can lead to various adverse hormonal effects, including sexual dysfunction, gynecomastia, amenorrhea, and galactorrhea (Cutler, 2003; Smith et al., 2002), and evidence from both medical and psychiatric populations supports an association between hyperprolactinemia and sexual dysfunction. However, it is still not clear to what extent sexual dysfunction is influenced directly by hyperprolactinemia (Haddad and Wieck, 2004). Several studies reported a relation between sexual dysfunction and prolactin levels (Arató et al., 1979; Bruke et al., 1994; Ghadirian et al., 1982; Smith et al., 2002). However, other studies, including the current findings, have failed to support an association between hyperprolactinemia and sexual dysfunction (Hamner, 2002; Kleinberg et al., 1999; Spollen et al., 2004). Several issues may explain these conflicting results. First, libido and orgasm are related to dopaminergic neuronal circuits, so dopamine blockade by antipsychotics may have an impact on libido and orgasm (Giuliano and Allard, 2001). Second, the secondary effects of prolactin elevation, that is, reduction of plasma levels of testosterone, estrogen, luteinizing hormone, or follicle-stimulating hormone, could lead to sexual side effects (Rinieris et al., 1989;

Table 3
Total NSFQ score and prolactin levels (ng/ml) in males and females.

Gender	Mean prolactin level (ng/ml)		Mean total NSFQ score		Stratified prolactin level (ng/ml)	n (%)	Mean total NSFQ score
							c
Males	21.5 ± 16.7	a	12.7 ± 5.5	b	0 - 20	57 (48.7)	11.9 ± 4.9
							13.4 ± 6.1
					20 - 50	55 (47.0)	
					50 - 100	5 (4.3)	14.4 ± 4.5
							d
Females	45.3 ± 46.7		14.0 ± 5.1		0 - 25	36 (46.2)	13.5 ± 6.2
					25 - 50	15 (19.2)	15.3 ± 3.1
					50 - 100	14 (17.9)	14.1 ± 3.5
					100 - 150	11 (14.1)	13.5 ± 5.3
					150 - 200	2 (2.6)	16.5 ± 0.7

In addition to the mean total score of NSFQ and prolactin levels (ng/ml) in males and females, the mean total NSFQ scores corresponding to stratified prolactin levels are presented. The mean prolactin level in females was significantly higher than in males ($^{a}t = 5.0357$, $p < 0.001$), but there was no significant difference in mean total NSFQ score between males and females ($^{b}t = 1.6743$, $p = 0.0957$). There were no significant differences in total NSFQ scores among stratified prolactin levels in males ($^{c}F = 1.219$ $df = 116$, $p = 0.299$) and females ($^{d}F = 0.486$, $df = 77$, $p = 0.746$).

Table 4
NSFQ total scores, total sexual dysfunction (%), and plasma prolactin levels (ng/ml) in each antipsychotic treatment group.

Males				
			Total sexual dysfunction	
Drug	Prolactin level a	NSFQ	≥3 (from mild to severe) n (%)	≥4 (moderate and severe) n (%)
Aripiprazole	5.2 ± 7.6	13.4 ± 5.0	11 (78.6)	5 (35.7)
Olanzapine	10.6 ± 7.4	13.1 ± 5.0	10 (66.7)	8 (53.3)
Polytherapy	23.2 ± 15.6	12.7 ± 6.1	29 (64.4)	15 (33.3)
Risperidone	29.8 ± 16.4	12.7 ± 5.4	27 (64.3)	19 (45.2)
Others	4.2 ± 0.4	8.0 ± 4.2	1 (33.3)	0 (0)

Females				
			Total sexual dysfunction	
Drug	Prolactin level f e	NSFQ	≥3 (from mild to severe) n (%)	≥4 (moderate and severe) n (%)
Aripiprazole	6.7 ± 7.6	13.5 ± 5.4	14 (82.4)	10 (58.8)
Olanzapine	23.4 ± 7.9	13.2 ± 3.2	5 (55.6)	3 (33.3)
Polytherapy	51.5 ± 45.2	12.7 ± 6.1	15 (83.3)	13 (72.2)
Risperidone	79.9 ± 48.9	13.9 ± 4.6	25 (92.6)	18 (66.7)
Others	17.6 ± 18.1	10.6 ± 6.1	3 (42.9)	2 (28.6)

There were significant differences in the prolactin levels among the antipsychotic groups of aripiprazole, olanzapine, polytherapy and risperidone in males ($F=13.251$, $df=114$, $p<0.001$, $^{a}p<0.001$, $^{b}p<0.001$, $^{c}p<0.026$, $^{d}p<0.001$) and females ($F=14.107$, $df=70$, $p<0.001$, $^{e}p<0.01$, $^{f}p<0.001$, $^{g}p<0.01$) subjects. The total NSFQ scores were not significantly different among the groups of aripiprazole, olanzapine polytherapy, and risperidone in males ($F=0.075$, $df=114$, $p=0.973$) and females ($F=1.537$, $df=70$, $p=0.213$). There was no significant difference in the frequency of total sexual dysfunction among the groups receiving aripiprazole, olanzapine polytherapy, and risperidone (males, from mild to severe, chi square 1.5508 $p=0.82$; moderate and severe, chi square 4.3366 $p=0.36$; females, from mild to severe, chi square 9.0318 $p=0.06$; moderate and severe, chi square 7.6454 $p=0.11$).

Smith et al., 2002). Third, noradrenergic and histaminergic effects are also suggested to change aspects of sexual performance (Meston and Frohlich, 2000). Fourth, the influence of the primary disease, treatment duration, age, and gender make it even more difficult to interpret the data (Smith et al., 2002). Finally, the different methodologies used to reveal sexual dysfunction likely lead to a major underestimation of the frequency of sexual dysfunction (Peuskens et al., 1998) Thus, clinicians should take these facts into account and pay attention to symptoms of sexual dysfunction in the presence or absence of hyperprolactinemia.

Previous studies suggested that the prolactin-raising drugs (e.g., risperidone) provoke significantly higher rates of sexual problems (40–60%) compared with prolactin-sparing drugs (e.g., quetiapine, ziprasidone, and aripiprazol) (<30%) (Knegtering et al., 2004, 2006; Montejo Gonzalez et al., 2005; Montejo and Rico-Villademoros, 2008a; Montejo et al., 2010a, 2010b; Serretti and Chiesa, 2011; Baggaley, 2008), whereas both our findings and those of Fujii et al. (2010) did not reveal any difference in the prevalence of sexual dysfunction among different medications in Japanese schizophrenic patients. The inconsistency between previous studies and the present study may be related to: (1) the small number of subjects on monotherapy and different numbers of subjects in the drug groups in our study, (2) the use of different rating scales (NSFQ ascertains information about sexual concerns indirectly, whereas the similar items on other scales are ascertained in a more direct manner. As a consequence, NSFQ may not be a strong instrument to detect such differences.), (3) different demographic data (the duration and treatment of illness in this study were more than 200 months, so there were many chronic patients in this study.), and (4) ethnic or cultural differences, (5) no baseline data (e.g., previous sexual functioning, sexual life, partner) before treatment with antipsychotics. However, our study revealed that patients taking antipsychotics reported to induce less sexual dysfunction have just as much sexual dysfunction as patients taking antipsychotics reported to induce more sexual dysfunction, suggesting that clinicians should pay attention to the clinical signs of sexual dysfunction regardless of the drugs patients are taking.

Our study has several limitations. First, sexual dysfunction was evaluated at only single time point, and this study was a cross-sectional study using a small clinical sample which composed of many chronic patients. So other factors but drug could have impact on the result of

this study, and it was difficult to comprehend the factor of drug perceptively. Moreover the number of patients on monotherapy was small and differed among the antipsychotic groups. However, our sample had adequate statistical power to effectively accept or reject the null hypothesis (males, $F = 13.251$, $p < 0.01$, power of test = 1.00; females, $F = 14.107$, $p < 0.01$, power of test = 1.00). Therefore, the current study could detect differences of prolactin level among drug groups accurately. Although we collected data regarding patients' ages, duration of illness, and duration of medication, no baseline data (e.g., previous sexual functioning, sexual life, partner) before treatment with antipsychotics were available and no inclusion and exclusion criteria were used in this study. These limitations might have impact on the results in this study different from prior studies. Sexual life could be influenced by many different factors that methodology may need to be quite strict. In addition, NSFQ may not be sufficient for assessing the orgasm, satisfaction and arousal due to the specific cultural aspects related to the Asian population and the further studies using other instruments should be performed in order to address this issue.

To clarify the relationship between prolactin levels and sexual dysfunction, an interventional study that investigates the effect of lowering prolactin levels on sexual dysfunction by switching antipsychotics is needed. Second, we have no data on other characteristics that might influence sexual dysfunction, including smoking status and other endocrinologic factors (such as testosterone and estradiol levels) and metabolic parameters like obesity or diabetes (Bhasin et al., 2007). Considering the important role of endocrinologic and metabolic factors in sexual dysfunction, further studies are needed to evaluate the impact of these factors (Wu et al., 2010). Third, although the patients who participated in the study were in stable condition, the impact of the disease itself on sexual dysfunction was not assessed. This factor should be included in a future study. Fourth arousal disturbances and orgasmic dysfunction are very relevant in the investigation of sexual functioning and these results are needed to obtain and clarify accurate sexual information, but these factors were not asked directly at NSFQ (There is item of sexual arousal in female NSFQ). We think that this fourth limitation might be a strong limitation and have impact on the result in this study. In order to address these issues, we are planning to conduct study of sexual function using SALSEX or other scale together with NSFQ and in order to improve performance of NSFQ.

5. Conclusion

This study is the first survey using NSFQ to estimate sexual dysfunction. Results showed a high prevalence of sexual dysfunction and hyperprolactinemia in Japanese schizophrenic patients, as with previous studies. Clinicians should pay careful attention to patients' sexual dysfunction to improve their QOL and adherence to therapy.

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References

Aizenberg D, Zemishlany Z, Dorfman-Etrog P, Weizman A. Sexual dysfunction in male schizophrenic patients. J Clin Psychiatry 1995;56(4):131–41.
Arató M, Erdös A, Polgár M. Endocrinological changes in patients with sexual dysfunction under long-term nueroleptic treatment. Pharmakopsychiatry Neuropsyachopharmakol 1979;12:426–31.
Baggaley M. Sexual dysfunction in schizophrenia: focus on recent evidence. Hum Psychopharmacol 2008;23:201–9.
Bhasin S, Enzlin P, Coviello A, Basson R. Sexual dysfunction in men and women with endocrine disorders. Lancet 2007;369(9561):597–611.
Bruke MA, McEvoy JP, Ritchie JC. A pilot study of a structured interview addressing sexual function in men with schizophrenia. Biol Psychiatry 1994;35:32–5.
Clayton A, McGarvey EL, Clavet GJ. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. Psychopharmacol Bull 1997;33(4): 731–45.
Cutler AJ. Sexual dysfunction and antipsychotic treatment. Psychoneuroendocrinology 2003;28(Suppl. 1):69–82.
Fakhoury WK, Wright D, Wallace M. Prevalence and extent of distress of adverse effects of antipsychotics among callers to a United Kingdom National Mental Health Helpline. Int Clin Psychopharmacol 2001;16(3):153–62.
Fujii A, Fukukori N, Sugawara N, et al. Sexual dysfunction in Japanese patients with schizophrenia treated with antipsychotics. Prog Neuropsychopharmacol Biol Psychiatry 2010;34(2):288–93.
Ghadirian AM, Chouinafd G, Annable L. Sexual dysfunction and plasma prolactin levels in neuroleptic-treated schizophrenic outpatients. J Nerv Ment Dis 1982;170(8): 463–7.
Giuliano F, Allard J. Dopamine and sexual function. Int J Impot Res 2001;13:S18–28.
Gopalakrishnan R, Jacob KS, Kuruvilla A, Vasantharaj B, John JK. Sildenafil in the treatment of antipsychotic-induced erectile dysfunction: a randomized double-blind, placebo-controlled, flexible-dose, two-way crossover trial. Am J Psychiatry 2006;163(3):494–9.
Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs 2004;64:2291–314.
Halbreich U, Kinon BJ, Gilmore JA, et al. Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects. Psychoneuroendocrinology 2003;28: 53–67.
Hamner M. The effects of atypical antipsychotics on serum prolactin levels. Ann Clin Psychiatry 2002;14(3):163–73.
Kikuchi T, Iwamoto K, Sasada K, et al. Reliability and validity of a new sexual function questionnaire (Nagoya Sexual Function Questionnaire, NSFQ) for schizophrenic patients taking antipsychotics. Hum Psychopharmacol 2011;26(4–5): 300–6.
Kleinberg DL, Davis JM, de Coster R, Van Baelen B, Brecher M. Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol 1999;19: 57–61.
Knegtering R, Castelein S, Bous H, et al. A randomized open-label study of the impact of quetiapine versus risperidone on sexual functioning. J Clin Psychopharmacol 2004;24(1):56–61.
Knegtering H, Boks M, Blijd C, Castelein S, van den Bosch RJ, Wiersma D. A randomized open-label comparison of the impact of olanzapine versus risperidone on sexual functioning. J Sex Marital Ther 2006;32:315–26.
Kotin J, Wilbert DE, Verburg D, Soldinger SM. Thioridazine and sexual dysfunction. Am J Psychiatry 1976;133(1):82–5.
Lingjaerde O, Ahkfors UG, Bech P, et al. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987;334: 1-100.
McGahuey CA, Galenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 2000;26(1):25–40.
Melkersson K. Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients. J Clin Psychiatry 2005;66(6):761–7.
Meston CM, Frohlich PF. The neurobiology of sexual functioning. Arch Gen Psychiatry 2000;57:1012–30.
Montejo Gonzalez AL, Rico-Villademoros F, Tafalla M, Majadas S, the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. A 6-month prospective observational study on the effects of quetiapine on sexual functioning. J Clin Psychopharmacol 2005;25:533–8.
Montejo AL, Rico-Villademoros F, Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Psychometric properties of the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX) in patients with schizophrenia and other psychotic disorders. J Sex Marital Ther 2008a;34:227–39.
Montejo AL, Rico-Villademoros F, Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Changes in sexual function for outpatients with schizophrenia or other psychotic disorders treated with ziprasidone in clinical practice settings: a 3-month prospective, observational study. J Clin Psychopharmacol 2008b;28:568–70.
Montejo AL, Garcia M, Espada M, Rico-Villademoros F, Llorca G, Izquierdo JA. Psychometric characteristics of the psychotropic-related sexual dysfunction questionnaire. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunctions. Actas Esp Psiquiatr 2000;28:141–50.
Montejo AL, Riesgo Y, Luque J, et al. Observational, open-label, prospective multicenter study of sexual function in patients starting treatment with aripiprazole. Actas Esp Psiquiatr 2010a;38(1):13–21.
Montejo AL, Mjadas S, Rico-Villademoros F, et al. Frequency of sexual dysfunction in patients with a psychotic disorder receiving antipsychotics. J Sex Med 2010b;7: 3404–13.
Moreira Jr ED, Hartman U, Glasser D, Gimgell C, GSSAB Investigators 2005 Group. A population survey of sexual activity, sexual dysfunction and associated help-seeking behavior in middle-aged and older adults in Germany. Eur J Med Res 2005;10(10):434–43.
Moreira Jr ED, Brock G, Glasser D, Gingell C. Sexual activity, prevalence of sexual problems, and associated help-seeking patterns in men and women aged 40–80 years in Korea: data from the Global Study of Sexual Attitudes and Behaviors. J Sex Med 2006;66(3):331–8.
Olfson M, Uttaro T, Carson WH, Tafesse E. Male sexual dysfunction and quality of life in schizophrenia. J Clin Psychiatry 2005;66(3):331–8.
Peuskens J, Sienaert P, De Hert M. Sexual dysfunction: the unspoken side effect of antipsychotics. Eur Psychiatry 1998;13:23S–30S.

Rinieris P, Hatzimanolis J, Markianos M, Stefanis C. Effects of treatment with various doses of haloperidol on the pituitary–gonadal axis in male schizophrenic patients. Neuropsychobiology 1989;22:146–9.
Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. Int Clin Psychopharmacol 2011;26(3):130–40.
Smith S, Wheeler MJ, Murray R, O'Keane V. The effects of antipsychotic-induced hyperprolactinemia on the hypothalamic–pituitary–gonadal axis. J Clin Psychopharmacol 2002;22:109–14.
Spollen JJ, Wooten RG, Cargile C, Bartztolis G. Prolactin levels and erectile function in patients treated with risperidone. J Clin Psychopharmacol 2004;24(2):161–6.
Withersty DJ. A model for continuing education. Am J Psychiatry 1976;133:573–5.
Wolfe SD, Menninger WW. Fostering open communication about sexual concerns in a mental hospital. Hosp Community Psychiatry 1973;24:147–50.
Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–35.

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Wisconsin Card Sorting Test scores and clinical and sociodemographic correlates in Schizophrenia: multiple logistic regression analysis

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ABSTRACT

Objectives: This study investigated what clinical and sociodemographic factors affected Wisconsin Card Sorting Test (WCST) factor scores of patients with schizophrenia to evaluate parameters or items of the WCST.

Design: Cross-sectional study.

Setting: Patients with schizophrenia from three hospitals participated.

Participants: Participants were recruited from July 2009 to August 2011. 131 Japanese patients with schizophrenia (84 men and 47 women, 43.5 ±13.8 years (mean±SD)) entered and completed the study. Participants were recruited in the study if they (1) met DSM-IV criteria for schizophrenia; (2) were physically healthy and (3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy or mental retardation. We examined their basic clinical and sociodemographic factors (sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses and the positive and negative syndrome scale (PANSS) scores).

Primary and secondary outcome measures: All patients carried out the WCST Keio version. Five indicators were calculated, including categories achieved (CA), perseverative errors in Milner (PEM) and Nelson (PEN), total errors (TE) and difficulties of maintaining set (DMS). From the principal component analysis, we identified two factors (1 and 2). We assessed the relationship between these factor scores and clinical and sociodemographic factors, using multiple logistic regression analysis.

Results: Factor 1 was mainly composed of CA, PEM, PEN and TE. Factor 2 was mainly composed of DMS. The factor 1 score was affected by age, education years and the PANSS negative scale score. The factor 2 score was affected by duration of illness.

Conclusions: Age, education years, PANSS negative scale score and duration of illness affected WCST factor scores in patients with schizophrenia. Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

ARTICLE SUMMARY

Article focus

- To investigate relationships between Wisconsin Card Sorting Test (WCST) factor scores and clinical and sociodemographic factors in Japanese patients with schizophrenia using multiple logistic regression analysis.
- To show distribution of each WCST score for patients with schizophrenia.

Key messages

- Age, education years, positive and negative syndrome scale negative scale score and duration of illness affected two WCST factor scores.
- Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Strengths and limitations of this study

- We conducted principal component analysis and identified two WCST factors. Components of two WCST factors in this study were similar to previous studies.
- This is the first study to investigate relationships between WCST factor scores and clinical and sociodemographic factors in patients with schizophrenia.
- We identified a clinical and sociodemographic factor (duration of illness) that affected the WCST factor 2 score. This is a new finding.

INTRODUCTION

Cognitive impairment in patients with schizophrenia has been evaluated as an indicator of outcome regarding social functioning and quality of life.[1 2] It is reported that cognitive performance in patients with schizophrenia declines from prodrome to onset of schizophrenia (first episode).[3] Moreover, it is reported that decline of cognitive performance exists before onset of schizophrenia.[3] Many studies using brain imaging suggest that neurobiological changes in the brain are related to