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【講演】

[1] 野田隆政「身体疾患患者へのメンタルケアモデル開発に関するナショナルプロジェクトの進展」第 5 回全国都道府県臨床心理士会医療保険領域担当者研修会，東京，2014.12.7

3．その他

【マスメディアでの報道】

[1] 月刊 BOSS：4 月から健康保険の適用に光トポグラフィー検査ってなんだ？ 2014 年 6 月号 p72

[2] 野田隆政：臨・床・最・前・線「国立精神・神経医療研究センター病院　精神科」Depression Journal　2014 年 8 月号 Pp16-19

H．知的財産権の出願・登録状況

1．特許取得（予定含む）

[1] 桂卓成，木口雅史，佐藤大樹，敦森洋和，舟根司，川崎真護，野田隆政，中込和幸．精神疾患分類法、判別法及び判別基準作成及び学習システム．特願 2015-002557，2015 年 1 月 8 日

厚生労働科学研究委託費（障害者対策総合研究事業）
委託業務成果報告（業務項目）

認知機能および社会機能のマーカーの応用に関わる研究開発
－認知機能および社会機能の障害の電気生理学的指標に関わる研究開発－

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研 究 要 旨

本研究は、統合失調症患者の転帰を大きく左右する認知機能および社会機能的能力を反映する神経生物学的マーカーとして、P300、ミスマッチ陰性電位などの事象電位に注目し、認知機能や日常生活技能との関連を検討した。

A．研究目的

本研究は統合失調症の早期診断・治療に向けた神経生理学的指標の探索を目的として、事象関連電位（ERPs; event related potentials）の早期診断に対する有用性を検討する。これにより測定しうる各種の指標が、患者の状態や治療反応性の客観的な評価に資するかを検討する。さらに、脳画像解析、神経心理学的検査、社会認知機能検査を同時に施行し、それらの遂行成績との関連を調べる。このように病期進行の神経生物学的特徴を考察することにより、統合失調症の診断に役立つ鋭敏で特異的な生物学的指標を開発した。

B．研究方法

(1) 対象

本施設附属病院を受診した、Comprehensive Assessment of at risk mental state(CAARMS)による ARMS の診断基準（Yung et al., 2005）を満たした患者、あるいは、国際疾病分類（ICD-10）の診断基準を満たした統合失調症患者において、事象関連電位および神経心理学的検査、社会機能・認知機能検査を実施した。

検査は縦断的（ベースライン、6ヶ月、1年、2年、5年時点）で行う。

(2) 検査方法

P300,MMN（mismatch negativity;MMN）などの ERPs をデジタル脳波計、脳波用キャップ、および聴覚刺激発生装置を用いて計測する。P300 は音刺激に集中させた状態で測定するのに対し、MMN は集中させない状態で自動的な音韻のミスマッチの検出機能を測定する。このため MMN 測定時は無音のアニメーション映画に集中し音には注意を向けさせないようにする。

これらの ERP のベースライン時点での特徴と、フォローアップ時でどのように変化するかを調べた。

また、認知機能、社会機能の評価には The brief assessment of cognition in schizophrenia Japanese version (BACS-J) 、The schizophrenia cognition rating scale Japanese version (SCoRS-J)などの評価尺度を用いた。

（倫理面への配慮）

なお、本研究は当院倫理委員会の承認を得て行われた（精神病前駆期に対する治療法の開発；倫 198 号, 精神病性障害関連遺伝子の解析研究；遺 25-7 号）。患者（未成年者の場合は患者および保護者から）書面による同意を得た。

C．研究結果

① 臨床病期別の ERP 測定結果

ARMS 19 名、初発統合失調症(first episode schizophrenia; FES) 19 名、健常者 19 名、慢性期統合失調症（chronic schizophrenia; CS）19 名から ERP データを得た。ARMS 群において、持続長 MMN（duration MMN;dMMN)の振幅は、健常者より小さく、統合失調症患者より大きかった（Fz；健常者；-7.4 μV, ARMS -6.5 μV, FES -5.4 μV, CS -4.8 μV, $F(3,74)=8.32, p<0.001$）。ARMS を、後に統合失調症を発症した者（converter; Conv.）、発症しなかった者（non-converter; Non-C.）に分けて検討した結果、Conv.が有意に振幅が低かった（Fz； Conv. -4.7 μV, Non-C -7.0 μV）。また、Conv.と統合失調症、Non-C.と健常者の所見の類似性が示された。また、MMN に引き続いて現れる成分として、P3a、RON（reorienting negativity）があり MMN と同様、注意機能を反映するといわれている。これらの波形を総称して”MMN/P3a/reorienting complex”と呼ぶ。

P3a 振幅の差異は認められなかったが、RON 振幅は、F4,Fz において病期間の有意差が認められ、（それぞれ F4,Fz において $F(3,74)=4.19,3.14$；$p=0.009,0.03$、）Conv.-Non-C.間では有意傾向がみられた（F4； Conv. -3.1 μV, Non-C -4.5 μV、Fz；Conv. -2.8 μV, Non-C -4.6 μV）。全対象者の波形は図 1、ARMS は図 2 に示す。

② ARMS の縦断データ

ARMS について、縦断データの検討を行った。15 例の患者を対象とした。

MMN/P3a/reorienting complex を図 3 に示す。ベースラインとフォロー時では、dMMN・RON のの振幅の差は見られなかったが、P3a はフォロー時で振幅の増大が見られた（Fz； base 1.5±1.2 μV, follow 2.6±1.7 μV）。

更に図 4 で示したように P3a 振幅の変化（増大）は SCoRS（統合失調症患者の日常生活技能を測定する評価尺度）の変化（改善）と正の相関を示した（$Fz; r=0.594$, $p=0.032$）。

D．考察

これまで統合失調症のみならず精神病発症リスク状態でも dMMN 振幅が低下しているとする報告が複数みられるが我々の研究でも、同様の結果が得られた。

精神病発症リスク状態の患者をのちに統合失調症を発症した者と発症しなかった者に分けて検討すると、統合失調症を発症した者はベースライン時点での dMMN 振幅が低かった。これは、dMMN が統合失調症の素因を表現するバイオマーカーへとして応用できる可能性を示すものと考えらえた。

更に今回新たに MMN/P3a/reorienting complex 波形についても検討を加えた。その結果、RON 振幅も臨床病期との関連があり、有意傾向ではあったが、非発症群にくらべ発症群で振幅が低かった。今回は症例が少なく十分な検討には至らなかったが、RON も統合失調症のバイオマーカーへの応用が可能である可能性が示された。

ARMS の患者を縦断的に検討すると、dMMN、RON に違いはなく、P3a の振幅が増大していた。ARMS は、フォローアップ時点では種々の治療により症状が改善している者が大半であり、振幅の増大は SCoRS

の改善度と相関した。

この結果より、dMMN、RON が trait に近い値であるのに対し、P3a はより state 近い値ではないかと考えられた

E．結論

この研究より、ARMS の dMMN および、関連する ERP 所見が統合失調症の発症予測の指標となる可能性が示された。他のドメイン（認知機能、社会機能など）と組み合わせれば、より精緻な診断の一助となりうるかもしれない。

更に、dMMN・RON 縦断データはバイオマーカーとして応用できる可能性が示唆された。

F．健康危険情報

該当なし

G．研究発表

1．論文発表

【原著】

Higuchi Y., Seo T., Miyanishi T., Kawasaki Y., Suzuki M., Sumiyoshi T.: Mismatch negativity and P3a/reorienting complex in subjects with schizophrenia or at-risk mental state. Frontiers in Behavioral Neuroscience, 2014 13;8:172

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2)樋口悠子，住吉太幹．【症例編】IX認知機能の改善．メディカルレビュー社：大阪：2014．統合失調症ケーススタディー～症例が導く社会復帰・QOL 向上への道～：p153-5

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2)Higuchi Y., Seo T., Miyanishi T., Kawasaki Y., Suzuki M., Sumiyoshi T.: Mismatch negativity and P3a/reorienting complex in subjects with schizophrenia or at-risk mental state. the 9th International Conference on Early Psychosis, 2014, 11, 17-19：Tokyo.

3)樋口悠子，住吉太幹，瀬尾友徳，西山　志満子，宮西友広，鈴木道雄. 精神病発症リスク状態におけるミスマッチ陰性電位の縦断的な変化と日常生活技能との関連. 第 34 回日本社会精神医学会，2015, 3, 5-6：富山

4)樋口悠子，住吉太幹，瀬尾友徳，西山　志満子，鈴木道雄. 統合失調症および精神病発症リスク状態における MMN/P3a/reorienting complex の特徴. 第 10 回日本統合失調症学会. 2015，3，27-28，東京

H．知的財産権の出願・登録状況

該当なし。

図 1

全対象者の MMN/P3a/reorienting complex 波形

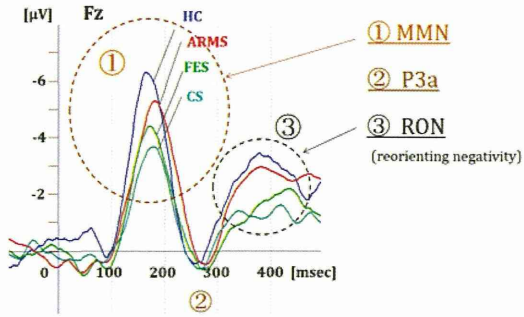


図 2

ARMS の MMN/P3a/reorienting complex 波形

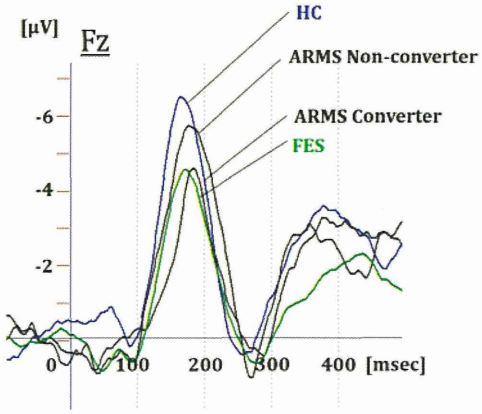


図 3

ARMS（縦断データ）の MMN/P3a/reorienting complex 波形

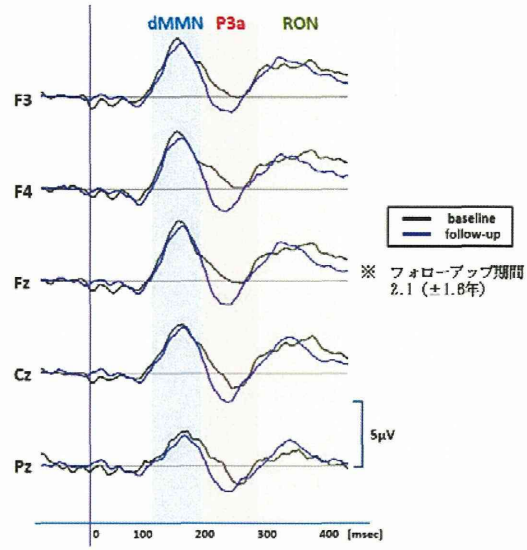
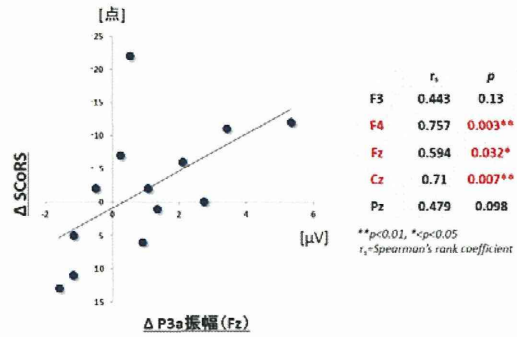


図 4

ARMS（縦断データ）の P3a と日常生活技能との関連



Ⅲ. 学会等発表実績　一覧

学 会 等 発 表 実 績

委託業務題目「統合失調症の認知および社会機能障害の神経生物学的マーカー開発についての研究」

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Event-related potentials in early phase schizophrenia; a feasible marker to predict psychosis?（口頭）	Sumiyoshi T	16th World Congress of Psychiatry	2014.9	国外
Research and Development Direction of Anti-Anxiety Drugs and the 5-HT Receptor.（口頭）	Sumiyoshi T.	海峡両岸医薬衛生交流協会	2014.11	国外
Mismatch negativity and P3a/reorienting complex in subjects with schizophrenia or at-risk mental state.(ポスター)	Higuchi Y., Seo T.,Miyanishi T., Kawasaki Y., Suzuki M., Sumiyoshi T.	The 9thInternational Conference on Early Psychosis, Tokyo	2014.11	国外
脳脊髄液モノアミン代謝産物と気質・性格（ＴＣＩ）との相関（ポスター）	Sumiyoshi T	16th World Congress of Psychiatry	2014.9	国内
統合失調症患者における内発的動機づけに関連した脳活動(口頭)	竹田和良、松元まどか、米田恵子、緒方洋輔、村上祐樹、村山航、花川隆、松元健二、中込和幸	第36回日本生物学的精神医学会学術総会	2014.9	国外
統合失調症患者における内発的動機づけに関連した脳活動(ポスター)	竹田和良，松元まどか，米田恵子，緒方洋輔，村上祐樹，村山航，下地啓五，花川隆，松元健二，中込和幸	包括脳ネットワーク冬のシンポジウム	2014.12	国内
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身体疾患患者のメンタルケアモデル開発ナショナルプロジェクトの進展.（口頭・シンポジウム）	野田隆政	第11回日本うつ病学会総会	2014.7	国内

抑うつ症状を合併したパーキンソン患者に対する近赤外線光トポグラフィー（NIRS）による評価の可能性. （ポスター）	横山仁史, 野田隆政, 中澤佳奈子, 瀬戸山志緒里, 村田美穂.	第11回日本うつ病学会総会	2014.7	国内
NIRSを用いたうつ病の重症度評価の可能性. （ポスター）	野田隆政, 中込和幸, 吉田寿美子, 功刀浩, 樋口輝彦.	第11回日本うつ病学会総会	2014.7	国内
気分障害患者における強迫性パーソナリティ傾向と認知機能との関連. （ポスター）	長島杏那, 松尾淳子, 木下裕紀子, 石田一希, 野田隆政, 樋口輝彦	第11回日本うつ病学会総会	2014.7	国内
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精神病発症リスク状態におけるミスマッチ陰性電位の縦断的な変化と日常生活技能との関連. （口頭）	樋口悠子, 住吉太幹, 瀬尾友徳, 西山　志満子, 宮西友広, 鈴木道雄.	第34回日本社会精神医学会, 富山	2015.3	国内
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臨床試験における認知機能評価. 治験教育セミナー. （口頭）	中込和幸、住吉太幹	第24回日本臨床精神神経薬理学会･第44回日本神経精神薬理学会合同年会	2014.11	国内

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Utility of the UCSD performance-based Skills Assessment-brief Japanese version: discriminative ability and relation to neurocognition.	Sumiyoshi C., Takaki M., A., Okahisa Y., Patterson T. L.	Schizophrenia Research Cognition	2014	国外
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Replication and cross-phenotype study based upon schizophrenia GWASs data in the Japanese population: support for association of MHC region with psychosis.	Saito T, Kondo K, Iwayama Y, Shimasaki A, Aleksic B, Yamada K, Toyota T, Hattori E, Esaki K, Ujike H, Inada T, Kunugi H, Kato T, Yoshikawa T, Ozaki N, Ikeda M, Iwata N.	Am J Med Genet B Neuropsychiatr Genet	2014.7	国外
Serum proBDNF/BDNF and response to fluvoxamine in drug-naïve first-episode major depressive disorder patients.	Yoshimura R, Kishi T, Hori H, Atake K, Katsuki A, Nakano-Umene W, Ikenouchi-Sugita A, Iwata N, Nakamura J	Annals of General Psychiatry	2014	国外

Characteristic distributions of regional cerebral blood flow changes in major depressive disorder patients: a pseudo-continuous arterial spin labeling (pCASL) study.	Ota M, Noda T, Sato N, Hattori K, Teraishi T, Hori H, Nagashima A, Shimoji K, Higuchi T, Kunugi H.	Journal of Affective Disorder, 165: 59-63	2014	国外
Mismatch negativity and P3a/reorienting complex in subjects with schizophrenia or at-risk mental state.	Higuchi Y., Seo T., Miyanishi T., Kawasaki Y., Suzuki M., Sumiyoshi T.	Frontiers in Behavioral Neuroscience	2014	国外
Neuroimaging-aided differential diagnosis of the depressive state	Ryu Takizawa, Masato Fukuda, Shingo Kawasaki, Kiyoto Kasai, Masaru Mimura, Shenghong Pu, Takamasa Noda, Shin-ichi Niwa, Yuji Okazaki, j on behalf of the Joint Project for Psychiatric Application of Near-Infrared Spectroscopy (JPSY-NIRS) Group	NeuroImage. 85(1) :498-507	2014	国外
Characteristic distributions of regional cerebral blood flow changes in major depressive disorder patients: a pseudo-continuous arterial spin labeling (pCASL) study.	Ota M, Noda T, Sato N, Hattori K, Teraishi T, Hori H, Nagashima A, Shimoji K, Higuchi T, Kunugi H.	Journal of Affective Disorder, 165: 59-63	2014	国外
事象関連電位から見る疾患	樋口悠子、住吉太幹、鈴木道雄	福田正人　編. 中山書店：精神疾患の脳画像ケースカンファレンス	2014	国内

Ⅳ. 研究成果の刊行物・別刷

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Serotonin and dopamine receptors in motivational and cognitive disturbances of schizophrenia

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Negative symptoms (e.g., decreased spontaneity, social withdrawal, blunt affect) and disturbances of cognitive function (e.g., several types of memory, attention, processing speed, executive function, fluency) provide a major determinant of long-term outcome in patients with schizophrenia. Specifically, motivation deficits, a type of negative symptoms, have been attracting interest as (1) a moderator of cognitive performance in schizophrenia and related disorders, and (2) a modulating factor of cognitive enhancers/remediation. These considerations suggest the need to clarify neurobiological substrates regulating motivation. Genetic studies indicate a role for the monoamine systems in motivation and key cognitive domains. For example, polymorphism of genes encoding catecholamine-O-methyltransferase, an enzyme catabolizing dopamine (DA), affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion. On the other hand, motivation to maximize rewards has been shown to be influenced by other genes encoding DA-related substrates, such as DARPP-32 and DA-D_2 receptors. Serotonin (5-HT) receptors may also play a significant role in cognitive and motivational disabilities in psychoses and mood disorders. For example, mutant mice over-expressing D_2 receptors in the striatum, an animal model of schizophrenia, exhibit both decreased willingness to work for reward and up-regulation of 5-HT_{2C} receptors. Taken together, genetic predisposition related to 5-HT receptors may mediate the diversity of incentive motivation that is impaired in patients receiving biological and/or psychosocial treatments. Thus, research into genetic and neurobiological measures of motivation, in association with 5-HT receptors, is likely to facilitate intervention into patients seeking better social consequences.

Keywords: serotonin, 5-HT receptors, motivation, cognition, schizophrenia, dopamine, negative symptoms, psychosis

INTRODUCTION

Disturbances of mental processes, including cognitive function (e.g., several types of memory, attention, processing speed, and executive function, fluency) and motivation characterize many of the psychiatric illnesses, such as schizophrenia, mood disorders, and substance abuse (Simpson et al., 2011; Choi et al., 2014; Sumiyoshi, in press). Recently, the development of biological (e.g., pharmacotherapy and brain stimulation) and psychosocial (e.g., cognitive rehabilitation) interventions is targeting social function/adaptation as an important outcome measure (Harvey et al., 2011; Leifker et al., 2011). In this context, negative symptoms (decreased spontaneity, social withdrawal, and blunt affect) and cognitive impairment provide a major determinant of long-term outcome. Specifically, motivation deficits have been attracting interest as a moderator of (1) cognitive performance in patients with schizophrenia and related disorders, and (2) beneficial influence of cognitive enhancers/remediation (Fervaha et al., 2014; Strauss et al., 2014). These considerations suggest the need to clarify neurobiological substrates regulating motivation for improving quality of life in a rational and effective manner.

We herein present a theory/hypothesis that the research into genetic and neurobiological measures of motivation, linked to serotonin (5-HT) receptors, would facilitate treatment of patients with schizophrenia or other psychiatric illnesses.

MOTIVATIONAL DISTURBANCES IN SCHIZOPHRENIA

Schizophrenia is characterized by a range of symptoms, e.g., positive symptoms (delusions, hallucinations, thought disorders), negative symptoms, mood symptoms, and cognitive impairment. Specifically, there is a suggestion that negative symptoms can be separated into two domains; (1) a motivational dimension, consisting of avolition, anhedonia, and asociality, and (2) a diminished expressivity dimension, consisting of restricted affect and alogia (Strauss et al., 2014). There is a general consensus that motivational disturbances may overlap some (e.g., anhedonia), but not all (e.g., blunt affect, alogia) aspects of negative symptoms. The former dimension has been considered to be of greater importance in terms of functional outcome, quality of life, and recovery from the disease (Strauss et al., 2014). Whether other aspects of symptomatology of schizophrenia (e.g., mood

symptoms) may substantially affect motivation in patients or vulnerable people remains to be determined (Schlosser et al., 2014).

DOPAMINE (DA) SYSTEMS GOVERNING MOTIVATION AND COGNITION

The neural basis for intrinsic motivation has been an issue of extensive research. For example, activity of the anterior striatum and prefrontal cortex (PFC), measured by the functional MRI, has been shown to be associated with intrinsic motivation (Murayama et al., 2010). This line of anatomical evidence is consistent with genetic studies indicating a role for the monoamine systems in cognition and motivation, as discussed below.

The Val158Met polymorphism of the genes encoding catecholamine-O-methyltransferase (COMT), an enzyme catabolizing DA, affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion (Egan et al., 2001). Thus, individuals with the val/val carriers in *COMT* show greater efficacy of the enzyme, leading to decreased DA levels in the PFC. The enzyme has also been suggested to mediate uncertainty-based exploration that is linked to DA levels in the PFC. For example, individuals with at least one met-allele show enhanced exploration compared to those with val/val genotype (Frank et al., 2007).

On the other hand, motivation to maximize rewards has been shown to be influenced by other DA-related genes expressed in the striatum/nucleus accumbens (NAc). Specifically, reward learning and negative reward avoidance are affected by genotypes of a polymorphism (rs907094. A/G) of the gene encoding DARPP-32 (a protein required for synaptic plasticity and reward learning mediated by DA-D_1 receptors) and the D_2 receptor (related to avoidance of negative outcomes), respectively (Frank et al., 2007; Klein et al., 2007). Thus, individuals with T/T genotype show greater expression of mRNA for the DARPP-32 gene, leading to greater performance to maximize rewards compared to C-allele carriers (reviewed in Frank et al., 2009). Similarly, T/T carriers of genes encoding D_2 receptors are associated with greater density of these receptors in the striatum and greater likelihood to maximize rewards (Hirvonen et al., 2004; Frank et al., 2007). A recent study (Simpson et al., 2013) reported that overexpression of D_3 receptors, a member of the D_2 receptor family, in the striatum selectively impaired incentive motivation, as measured by an operant task.

The mechanisms by which DA receptors govern motivation and cognitive functions may involve timing perception. For example, genetically-engineered mice overexpressing D2 receptors in the striatum have been shown to elicit impaired working memory, behavioral flexibility and sensorimotor gating, i.e., behavioral abnormalities reminiscent of schizophrenia (Kellendonk et al., 2006). These model animals also demonstrate reduced motivation, as well as alteration of interval timing organization, as measured by the operant timing task (Drew et al., 2007). Further studies indicate that the impaired timing in these mutant mice mediates the ability of decreased motivation to worsen cognitive functions, including working memory and attention (Ward et al., 2009). These lines of evidence suggest a strategy for the intervention into motivational disturbances, in terms of biological and/or tailor-made treatments.

Figure 1 summarizes a concept about how genes encoding these DA-related substrates contribute to cognitive and motivational behaviors.

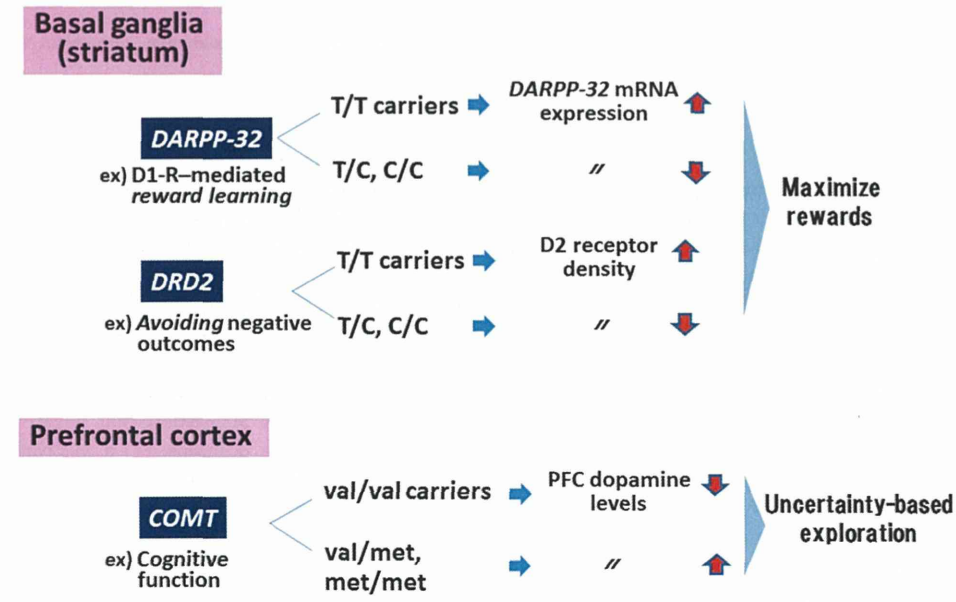

FIGURE 1 | Genes in the dopaminergic motivational system. Polymorphisms of genes encoding *DARPP-32* and dopamine (DA)-D_2 receptors *(DRD2)* affect behaviors to maximize rewards, while the polymorphism in *COMT* are associated with uncertainty-based exploration. Information in the Figure was extracted from Frank et al. (2009).

5-HT RECEPTOR SUBTYPES IN MOTIVATION-RELATED BEHAVIORS

5-HT receptors, e.g., 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} subtypes, may also play a role in cognitive and motivational disabilities in psychoses and mood disorders (Meltzer and Massey, 2011; Newman-Tancredi and Albert, 2012; Ohno et al., 2012). For example, several antipsychotic and antidepressant drugs have been suggested to ameliorate negative symptoms and mood disturbances, partly through actions on 5-HT_{1A} and 5-HT_{2A} receptors (Newman-Tancredi and Albert, 2012; Ohno et al., 2012; Sumiyoshi et al., 2013; Sumiyoshi, 2014). Clozapine, the prototype of atypical antipsychotic drugs, which is most effective in treating negative symptoms, may act as an inverse agonist on 5-HT_{2C} receptors (Meltzer and Massey, 2011).

Data from recent investigations support the contribution of 5-HT receptors to motivational behaviors. For example, mutant mice over-expressing D_2 receptors in the striatum, exhibit both decreased willingness to work for reward and up-regulation of 5-HT_{2C} receptors (Simpson et al., 2011). Furthermore, increased D_1, D_2 and 5-HT_{2C} receptors co-exist in mice mis-expressing ADAR2, an RNA-editing enzyme, and these animals elicit altered expression of reward-related mRNAs in the brain (Akubuiro et al., 2013). Collectively, these observations indicate the importance of some 5-HT receptor subtypes, e.g., 5-HT_{2C} receptors, in the pathophysiology and treatment of motivational disturbances associated with psychoses (**Figure 2**).

The role for 5-HT_{2C} receptors in psychiatric symptoms relevant to functional outcome is also supported by observations in mice whose 5-HT-synthesizing enzyme (tryptophan hydroxyxlase-2) was genetically engineered (Del'Guidice et al., 2014). Thus, treatment with the 5-HT_{2C} agonist CP809,101 ameliorated impairments in cognitive flexibility and reversal learning in these mutant animals (Del'Guidice et al., 2014).

As noted above, up-regulation of 5-HT_{2c} receptors in the striatum may be associated with a decrease in incentive motivation (Simpson et al., 2011). Further, 5-HT_{2c} receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also have been suggested to regulate motivation by modulating transmissions to NAc (Bubar et al., 2011) (**Figure 2**). It should be noted that a proportion of NAc-projecting VTA neurons may release both DA and GABA (Bubar et al., 2011). Altered balance in this complicated 5-HT_{2c} receptor-associated network is postulated to cause reward-related disorders, such as schizophrenia, depression, and addiction (Bubar et al., 2011).

Other 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A}receptors, may directly or indirectly influence this neural system for motivational behaviors as well. For example, 5-HT_{1A} receptor gene promotor polymorphism (rs6295, C-1019G) has been associated with treatment effects on negative symptoms of schizophrenia (Reynolds et al., 2006). **Figure 2** illustrates a putative neural network mediating motivational behaviors in relation to 5-HT receptors, which, together with

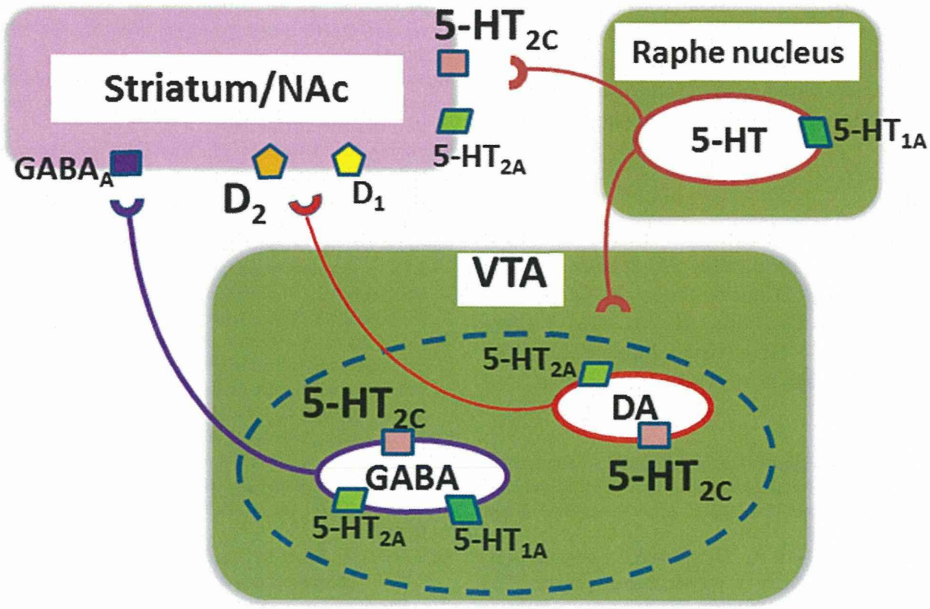

FIGURE 2 | A putative neural network mediating motivational behaviors in relation to serotonin (5-HT) receptors. (1) Up-regulation of 5-HT_{2c} receptors in the nucleus accumbens (NAc)/striatum may be associated with a decrease in incentive motivation in mutant mice over-expressing dopamine (DA)-D_2 receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). SB242084, a selective *ant*agonist at these receptors, increases incentive motivation in these model mice. (2) 5-HT_{2c} receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also affect motivation by modulating transmissions to NAc, including actions on D_1 and D_2 receptors (Bubar et al., 2011). The dotted line indicates that a proportion of NAc-projecting VTA neurons releases both DA and GABA (Bubar et al., 2011). (3) Other 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A}, may also directly or indirectly regulate this neural system of motivational behaviors.

Figure 1 (upper part), may suggest the contribution of DA-5-HT interactions.

CLINICAL PERSPECTIVES AND FUTURE DIRECTIONS

Based on the discussions so far, drugs acting on some 5-HT receptor subtypes, particularly, 5-HT_{2C} receptors, are likely to improve motivational deficits in individuals with schizophrenia. For example, SB242084, a selective *ant*agonist at 5-HT_{2C} receptors, has been shown to increase incentive motivation in mice over-expressing D_2 receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). By contrast, the 5-HT_{2C} receptor *ago*nist CP809,101 has been demonstrated to enhance performance on some cognitive tasks in mice with decreased 5-HT synthesis (Del'Guidice et al., 2014). These preclinical observations warrant clinical studies of the effect of agents for specific 5-HT receptor subtypes, e.g., 5-HT_{2C} receptors, on motivational and cognitive disturbances. Specifically, it is important to see if such putative pro-motivation drugs will lead to improvement of functional outcome affected by cognitive function on which such compounds might act in variable directions.

In view of a possible influence of motivation on cognitive training, it may be interesting to determine if augmentation with pro-motivation compounds, e.g., 5-HT_{2C} agents, would provide additional merits for cognitive and functional outcome in patients with schizophrenia. Also, whether genetic variations regarding 5-HT and/or DA receptors affect motivational response to treatment with existing pharmacological or psychosocial interventions deserves further study.

In summary, genetic predisposition related to 5-HT and DA receptors may mediate the diversity of incentive motivation that is impaired in patients with schizophrenia. This concept is expected to facilitate rational treatment with biological and/or psychosocial tools to improve social consequences for people with psychiatric illnesses.

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Utility of the UCSD Performance-based Skills Assessment-Brief Japanese version: discriminative ability and relation to neurocognition

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ABSTRACT

The UCSD Performance-based Skills Assessment Brief (the UPSA-B) has been widely used for evaluating functional capacity in patients with schizophrenia. The utility of the battery in a wide range of cultural contexts has been of concern among developers. The current study investigated the validity of the Japanese version of the UPSA-B as a measure of functional capacity and as a co-primary for neurocognion. Sixty-four Japanese patients with schizophrenia and 83 healthy adults entered the study. The Japanese version of the UPSA-B (UPSA-B Japanese version) and the MATRICS Cognitive Consensus Battery Japanese version (MCCB Japanese version) were administered. Normal controls performed significantly better than patients, with large effect sizes for the Total and the subscale scores of the UPSA-B. Receiver Operating Characteristic (ROC) curve analysis revealed that the optimal cut-off point for the UPSA-B Total score was estimated at around 80. The UPSA-B Total score was significantly correlated with the MCCB Composite score and several domain scores, indicating the relationship between this co-primary measure and overall cognitive functioning in Japanese patients with schizophrenia. The results obtained here suggest that the UPSA-B Japanese version is an effective tool for evaluating disturbances of daily-living skills linked to cognitive functioning in schizophrenia, providing an identifiable cut-off point and relationships to neurocognition. Further research is warranted to evaluate the psychometrical properties and response to treatment of the Japanese version of the UPSA-B.

1. Introduction

There has been a growing concern over functional outcome in patients with schizophrenia (Burns and Patrick, 2007) since its inclusion in DSM-III or later editions. Functional outcome refers to a wide range of real-world functioning including residential independence, employment, daily-living skills (e.g. financial management, telephone communication), or social activities (Harvey and Bellack, 2009). The role of cognitive deficits in impaired functional outcome has been well-conceptualized with the advent of the Measurement and Treatment Research to Improve in Schizophrenia Consensus Cognitive Battery (Nuechterlein and Green, 2006; Nuechterlein et al., 2008). Although the initial purpose of the MCCB was to provide a comprehensive battery sensitive to neurocognitive improvement by drug treatment, co-primary measures, predictive of real-world functioning, were also requested to accommodate the development of cognitive enhancers (Buchanan et al., 2011).

Performance-based batteries such as the UCSD Performance-based Skills Assessment-Brief (Mausbach et al., 2007) have been shown to provide a potential co-primary measure, satisfying 1) test–retest reliability, 2) a moderate practice effect, 3) a high completion rate, 4) a good correlation with neurocognitive performance, and 5) a discriminability for residential status and social involvement, such as work (Leifker et al., 2009, 2010; Mausbach et al., 2007, 2008, 2011; Olsson et al., 2012).

As the name suggests, tasks in the UPSA-B are role-played using props (e.g. money, an invoice, a letter, and a telephone etc.) to evaluate functional capacity (competence) in daily-living contexts (Mausbach et al., 2007, 2011). The battery consists of two subscales: Finances (e.g. counting money, bill payment) and Communication (e.g. using a phone). They were extracted from the full version of the original UPSA (Patterson et al., 2001) based on factor analysis (Mausbach et al., 2007). Due to its conciseness (approximately 10–15 min) and effectiveness as a co-primary measure, the battery has been widely used in the US, and has been introduced in Europe (Sweden: Harvey et al., 2009a; Olsson et al.,

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Table 1
The UPSA-B studies in the US and other countries.

Country	Study	Participants[a]	N	UPSA-B[b]			Sample[c]
				Total	Finances	Communication	
US	Bowie et al., 2010	SCZ BD	161 130	69.9 88.5	–	–	Patients with schizophrenia or schizoaffective disorder who were community living with Ashkenazi Jewish backgrounds. Results were obtained from the analyses of subsamples
	Green et al., 2011	SCZ	162	73.0	–	–	Recruited at the Validation of Intermediate Measure (VIM) study under the MATRICS initiative
	Harvey et al., in press	SCZ BD	3445 4624	74.0 83.0	–	–	Enrolled in the genomic study based on a Veterans Administration initiative (CSP#572)
	Keefe et al., 2011	SCZ	323	70.0	–	–	Participants were in a large multi-site trial assessing the comparative effects of antipsychotic treatment with lurasidone or risperidone
	Leifker et al., 2009	SCZ	194	72.2	–	–	Older patients with schizophrenia enrolled in longitudinal study of the course of cognitive and functional status. They were recruited at Mt. Sinai School of Medicine or other hospitals
	Leifker et al., 2010	SCZ (Mt. Sinai) SCZ (UCSD) NC	238 116 109	68.7[d] 56.5 84.5	–	–	Part of data was from Leifker et al., 2009 Recruited from Board and Care facilities in San Diego who enrolled in Functional Adaptation Skills Training Healthy subjects recruited at a naturally occurring retirement community (NORC) in Manhattan
	Mausbach et al., 2007	Independent living SCZ Non-independent living SCZ	99 335	72.5 54.5	–	–	Recruited at the UCSD Advanced Center for Interventions and Services Research. A subset of participants was part of the Functional Adaption Skills Training (FAST) study (Patterson et al., 2006)
	Mausbach et al., 2008	Assisted-living, SCZ, Schizoaffective Community-living SCZ, Schizoaffective	163 73	53.9 54.7	–	–	Part of data was from the FAST study
China	McIntosh et al., 2011	SCZ (Chinese) BD (Chinese) Major depression (Chinese) NC (Chinese)	272 61 50 284	37.6 55.2 47.9 64.3	–	–	Inpatients treated at a municipal psychiatric hospital in Beijing
India	Velligan et al., in press	SCZ (Indian)	160	67.6	–	–	Recruited from 6 different sites recommended by the MATRICS Scientific Advisory Board
US	Harvey et al., 2011	SCZ (Atlanta Skyland Trail) SCZ (Atlanta VA Medical Center)	55 40	75.5 81.7	40.1	–	Enrolled in the Validation of Everyday Real-World Outcomes (VALERO) study (Harvey et al., 2011, 2013)
	Harvey et al., 2013	SCZ (UCSD Outpatients Psychiatric Services)	100	75.3			
	Burton et al., 2013	SCZ, Schizoaffective	183		40.0	36.4	Data from the three different services referred in the VALERO study (Harvey et al., 2011, 2013)
	Harvey et al., 2009b	SCZ, Schizoaffective	236	68.8	–	–	Schizophrenia or schizoaffective participants in a longitudinal study of cognitive and functional status. Outpatients recruited from several sites in New York and its suburbs
	Harvey et al., 2009a	SCZ	244		37.4	31.5	Data from the same general data set in Harvey et al., 2009a,b
	Mausbach et al., 2010	SCZ BD	116 89	75.6 88.7	39.5 45.7	36.1 43.0	Data from the same resource in Bowie et al., 2010
	Mausbach et al., 2011	SCZ	367	77.5	41.1	36.4	
Sweden	Harvey et al., 2009a	SCZ (Swedish)	146	68.9	38.7	30.9	Outpatients recruited at a country council-founded clinic at NU Health Care Hospital
	Olsson et al., 2012	SCZ, Schizoaffective, Delusional (Swedish)	211	69.4	38.8	30.6	Participants were in the study of Clinical Long-term Investigation of Psychosis in Sweden (CLIPS)
Denmark	Vesterager et al., 2012	First episode SCZ (Danish)	117	77.5	40.2	37.3	Participants were in the multi-site randomized clinical trial for cognitive remediation program (the NEUROCOM trial)

[a] SCZ: schizophrenia, BD: bipolar disorder, NC: normal controls.
[b] MAX score: Total = 100, Finances = 50, Communication = 50.
[c] Patients were mostly outpatients except for McIntosh et al., 2011.
[d] A base line score.

2012; Denmark: Vesterager et al., 2012) and Asia (China: McIntosh et al., 2011; India: Velligan et al. in press) (Table 1). Also, the Japanese version (Sumiyoshi et al., 2011) is under standardization.

Although the UPSA-B has promise for assessing functional capacity, some issues remain under consideration in developing its Japanese version. First, the normative performance on the Japanese version needs to

be clarified. To date, several studies have presented data of a normal population (Leifker et al., 2010; McIntosh et al., 2011). According to these reports, the achievement of the normal samples ranges from 60 to 85 (Table 1), which may be affected by age and educational attainment. The study with the US samples (Leifker et al., 2010) presented scores of elderly healthy people (the mean age = 68.0) with large effect sizes between schizophrenia patients (d = 0.90–1.58 across multiple sites). On the other hand, Chinese control subjects who had relatively low levels of average educational attainment (Mean = 8 years) elicited a considerably lower score (64.3) (McIntosh et al., 2011), while the dissociation from normal controls (d = 1.08) was the same degree as that in the US study (Leifker et al., 2010).

The normative performance differentiating between normal and clinical samples can also be discussed from the view point of independency of living. The initial development study of the UPSA-B (Mausbach et al., 2007), examined a cut-off point classifying patients with schizophrenia into independent- versus non-independent living groups. A score of around 60 was estimated as the optimal cut-off, suggesting that patients above that have the capacity to live independently as a part of the normal population. Given the rather wide range of scores of the achievement related to the standard, an optimal cut-off point, differentiating normal subjects from patients, needs to be determined for the Japanese version of the UPSA-B. Specifically, data from relatively younger (30–50 years old) normal samples are of concern, which has not been addressed in previous studies.

Second, the possible influence of the cultural or socio-economical backgrounds needs to be considered. Cross-cultural adaptability of functional outcome measures including the UPSA-B has been discussed among its developers (Gonzalez et al., 2013; Harvey and Velligan, 2011; Velligan et al., 2012). Ratings by experts in different countries including Europe, Russia, and Asia resulted in a relatively poorer cultural adaptability of the UPSA-B compared to the case in the US, due probably, to the difference in daily-living standards. Specifically, Mexico, India, and China presented the greatest challenges in adaptation (Velligan et al., 2012). On the other hand, the UPSA-B may be well accommodated in countries with relatively uniformly westernized living environments like Japan.

Third, the Japanese version of the UPSA-B is expected to serve as an effective co-primary measure for standard neurocognitive batteries such as the MCCB, as shown by previous studies (Green et al., 2011). Accordingly, the correlation with cognitive functioning needs to be evaluated as part of the development of the UPSA-B_J.

The purposes of the current study were to address those issues in showing the utility of the UPSA-B in Japan. First, the performance on the UPSA-B was compared between young or middle-aged normal controls and patients with schizophrenia. A cut-off point differentiating normal controls from patients was also determined. In addition, profiles of the task performance were produced to see if the domain- and task-specific difficulties exist in both groups. Finally, the relation to neurocognitive functioning, as assessed by the MCCB-J, was investigated to confirm its validity as a co-primary measure.

2. Methods

2.1. Participants

Sixty-four Japanese patients with schizophrenia and 83 healthy adults entered the study. Demographic and clinical profiles of the participants are summarized in Table 2. Patients were outpatients treated in Okayama University Hospital, and public or private hospitals in Toyama Prefecture. Diagnosis was established based on the DSM-IV-TR criteria by experienced psychiatrists using a structured interview, reference to medical history, and all available information. Patients known to be abusing alcohol or illicit drugs, or those with epilepsy, brain damage, or neurologic disorders, were excluded from the study. Psychiatric symptoms were assessed on the Brief Psychiatric Rating Scale (BPRS), 18-item version (Overall and Gorham, 1962).

Normal controls were recruited at Okayama University. The majority of them were office employees working in Okayama Prefecture. Written informed consent was obtained from all participants. The study protocol was approved by ethics committees at the respective study sites.

2.2. Measures

The Japanese versions of UPSA (Sumiyoshi et al., 2011) and MCCB were administered to all participants. The UPSA-B Japanese version was developed based on the international version of the UPSA-B, with some modifications to adjust for differences in everyday functional demands in Japan. It has been approved by developers after conducting two independent forward and back translations, reconciliation, and pilot testing on patients. The MCCB Japanese version has been shown to have good psychometric properties and validity (Kaneda et al., 2013).

Subscale scores of the two domains of the UPSA-B (i.e. Finances, Communication) were converted into the standard score ranging from 0 to 50, and thus the maximum of the Total score was 100 (Mausbach et al., 2007). Raw scores for the 10 subtests of the MCCB were converted to T-scores (mean = 50, SD = 10), out of which the seven domain scores were produced (Nuechterlein and Green, 2006). The T-score of each task corresponds to the domain score except for Speed of Processing (TMT, BACS SC, and Fluency) and Working Memory (LNS and WMS-SS), for which the composite scores were calculated by summing to the T-scores of tests included in those domains. The overall composite score

Table 2
Characteristics of participants.

	NC	SCZ	Effect size[a]	t/F (df)	p	Interpretations
N (M/F)	83 (71/12)	64 (34/30)	–			
Age	34.6 (9.4)[b]	35.2 (11.2)	–	t = −0.13 (143)	0.72	NC = SCZ
Education	16.6 (1.1)	13.6 (2.4)	–	t = 10.12 (143)	<0.000	NC > SCZ
Duration	–	9.7 (8.1)	–	–		
Drug (mg)[c]	–	444.8 (492.0)	–	–		
BPRS_Positive	–	10.0 (5.9)	–	–		
BPRS_Negative	–	7.5 (3.4)	–	–		
BPRS_Total	–	36.5 (12.8)	–	–		
MCCB Composite	510.5 (47.3)	376.3 (76.0)	2.1	F = 67.30 (1,140)	<0.000	NC > SCZ
UPSA-B Total	82.1 (8.6)	69.5 (13.7)	1.1	t = 6.80 (145)	<0.000	NC > SCZ
Finances	48.7 (3.3)	43.8 (7.8)	0.8	F = 46.24 (1,145)	<0.000	NC > SCZ
Communication	33.4 (7.6)	25.7 (9.5)	0.9			

NC: normal controls, SCZ: patients with schizophrenia.
[a] Cohen's d for normal controls vs. patients.
[b] Mean (SD).
[c] CPZ equivalent.

was the sum of the seven domain scores (Kern et al., 2008; Nuechterlein and Green, 2006).

The formal Japanese version of the MCCB was not released at that moment, and thus, the *T*-scores of the Japanese version were produced based on the data obtained in a preliminary study for the development of the Japanese version; the normative group consisted of 85 healthy adults (mean age = 40.0, SD = 11.2, range 19–65) and the mean and the standard deviation of this group served as the reference for the *T*-score conversion. Age-correction was applied according to the regression method employed in the standardization study in the US (Kern et al., 2008). Although both age- and gender-corrections are recommended in the MCCB Manual (Nuechterlein and Green, 2006), only the former was applied due to limitations in the reference group at that moment.

2.3. Statistical analyses

SPSS ver. 17.0 (SPSS Inc.) was used for all the analyses except for the estimation of effect sizes.

2.4. Group comparisons

Demographic variables (age and education) and the UPSA-B Total score were compared by *t*-test. Two-way analysis of variance (Two-way ANOVA) was conducted for the group comparisons for the UPSA-B subscales with Group (normal controls vs. patients) as a between-subject factor while Subscale (Finances vs. Communication) as a within-subject factor. The MCCB composite score was compared by one-way analysis of covariance (ANCOVA) controlling education. Effect sizes (Cohen's *d*) were calculated by dividing the mean difference between normal controls and patients by a pooled SDs from the two groups.

2.5. ROC curve analyses

Receiver Operating Characteristic (ROC) curves analyses were conducted for the UPSA-B Total and subscale scores. Every possible cut-off point was specified at a specific sensitivity and 1 − specificity. Sensitivity corresponds to the 'hit' rate indicating the correct classification of normal subjects as a normal sample. 1 − specificity and specificity represent the 'false alarm (FA)' and 'correct rejection (CR)' rates, respectively. The former refers to the rate of misclassifying patients into the normal sample, while the latter means the rate of correctly determining patients. As for the measure of sensitivity, the area under curve (AUC) with the 95% confidential interval (95% CI) and *d'* (*d*-prime) (Gescheider, 1985) were calculated; larger values suggest better sensitivity. Optimal cut-off points were determined for the UPSA-B Total score, at which the sum of sensitivity (% of hit) and specificity (% of CR) was maximized (Youden's *J*: Youden, 1950); (Mausbach et al., 2011).

2.6. Profiles for the UPSA-B

Profiles were created to show domain- or task-specific performance in each group. The mean scores were calculated for each task (MAX = 1 except for one task with MAX = 2 in the Finance part), and were plotted on a horizontal axis scaled with task numbers.

2.7. Correlation analyses

Simple correlations (Pearson's *r*) were calculated between the UPSA-B Total score and the MCCB overall composite and seven domain scores.

3. Results

3.1. Group comparisons

Table 2 presents the statistical results for demographic variables and the performance on the UPSA-B and the MCCB. Age did not differ between groups ($t = -0.36$, $df = 143$, *n.s.*) while Education was significantly higher for normal controls ($t = 10.12$, $df = 143$, $p < 0.01$). The UPSA-B Total score ($t = 6.80$, $df = 145$, $p < 0.01$) and the MCCB composite score ($F = 67.30$, $df = 1, 140$, $p < 0.01$) were significantly higher for normal controls than Main effects of Group and Subscales of the UPSA-B were significant without an interaction effect; normal controls performed better than patients ($F = 46.24$, $df = 1, 145$, $p < 0.01$) on both Finances and Communication subscales, and the Finances score was higher than Communication in both groups ($F = 474.18$, $df = 1, 145$, $p < 0.01$).

Overall, relatively large ESs were obtained ($d \geq 0.8$), suggesting that substantial differences existed between normal controls and patients in measures of both functional capacity (UPSA-B) and neurocognition (MCCB) (Table 2).

3.2. ROC curve analyses

Fig. 1 illustrates ROC curves for the UPSA-B Total score. AUC of 0.77 (95%CI: 0.70–0.85) was significantly greater ($p < 0.001$) than that of no information (0.50). *d'* associated with this curve was estimated as 1.26.

The optimal cut-off point for the Total score (MAX = 100) was estimated as 77.8, at which sensitivity (hit rate) and 1 − specificity (FA rate) were 0.67 and 0.21, respectively. The results suggest that of all normal controls, 67% had the UPSA Total score of 77.8 or above, while of all patients, 89 (= 100 − 21)% scored below this score.

3.3. Profiles of the UPSA-B

Fig. 2 presents profiles of UPSA-B scores for normal controls (A) and patients with schizophrenia (B). Normal controls performed almost perfectly on the Finances part (Fig. 2A, the left section). Likewise, the patient group showed better performance on the Finances part (Fig. 2B, the left section) than the Communication part (Fig. 2B, the right part).

Both normal controls and patients tended to perform poorly on Task 13 (speaking on the phone with a name and an address given by the

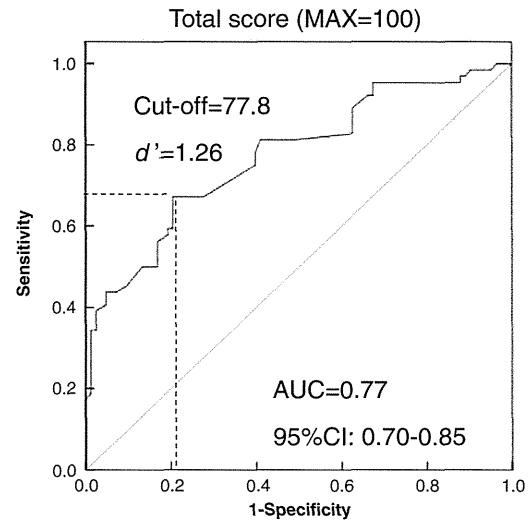

Fig. 1. ROC curves for UPSA-B Total score.