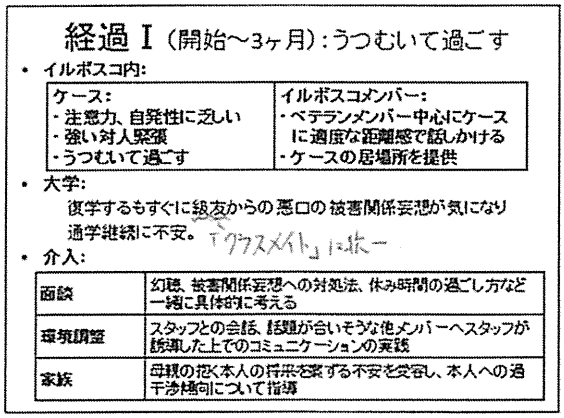

図２

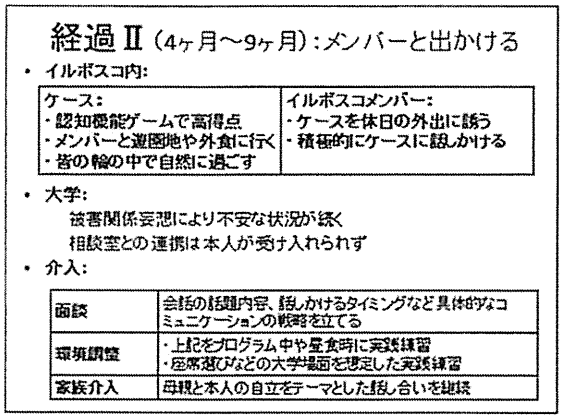

図３

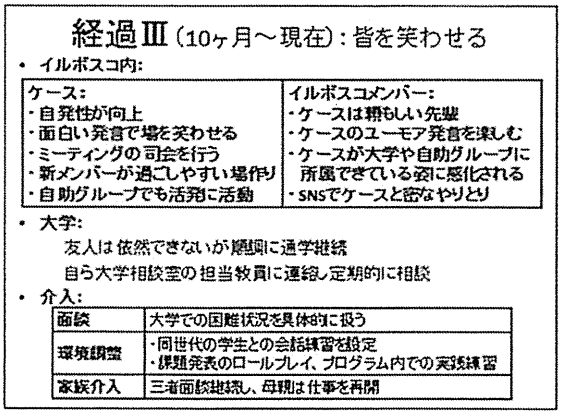

図４

の会話をスタッフが主導でコーディネートした。母親と本人とスタッフとで定期的に家族面接を行う中で、母親が本人の通学を心配するあまり緊密に連絡を取っている状況と、本人がその状況を苦痛に感じていることが確認された。このため、母親が本人に対し過干渉ぎみに関わっていることで、本人の対処技能の向上が阻害されている可能性について共有した。「本人の自立のために、自分で決めて自分で行動することが大切」であることを確認し合い、母親と本人との関わりにおいて適切な距離感を保つことについて指導を続けた。

＜介入経過Ⅱ（4ヶ月～9ヶ月）＞（図３）

認知機能ゲームやイルボスコ総会、イベント準備の話し合いの場面でも、自らの考えを表出するようになり、自発性の向上を認めた。チャレランの時間でも、問題を適切に聞き取り、より得点のとれる解答の導き方としての工夫をし、概ね高得点をおさめるようになった。また、イルボスコのメンバーに誘われ遊園地やカラオケに出かけるようになる等イルボスコ内での対人交流の幅が拡大し、周囲の配慮に支えられつつも集団の中で自然な振る舞いを見せるようになった。しかし、個別面談時には「大学の講義に出席する時に慣れない人の隣に座ることに緊張してしまい、どの席に座って講義を受けたら良いか分からない」と話していた。対人緊張とその不安に由来している状態と考え、「緊張しにくい座席のとり方」について話し合い対処法を講じた。また、より学生生活に沿った助言を継続的に得るために、本人に学生相談室教員との定期的な相談を勧めたが、本人は「どのように相談したら良いか分からない」と話していた。対人関係技能の乏しさに由来する状況と考え、実際の相談場面を想定した面接を繰り返し行った。家族面接では、依然母親が本人に対し状況確認を頻繁に行っており、そうした母親の心配を理解しつつも本人は重圧を感じている状況が確認されたため、引き続き「本人の自立のために、家族が本人の状態を見守るスタンスでいることが重要」であることを確認し、母親へ本人の状況を確認する頻度を減らすように勧めた。

＜介入経過Ⅲ（10ヶ月～15ヶ月）＞（図４）

自発性がさらに向上し、イルボスコのプログラム参加時や総会の時間に、面白くユーモアのある発言をし、皆を笑わせるようになり、ミーティングの司会等人前に出る係も積極的に行うようになった。又、自分が受けてきたように利用開始して慣れないメンバーの世話も行う中で、メンバー達

にとっては頼もしい先輩的存在となっていった。大学での友人は依然として作れていないものの、イルボスコ以外の自助グループにも所属するようになった。ブログ更新の係を担当する、一緒に旅行に行く等交流範囲の拡大を認め、通学時の不安感も減弱した。また、自ら学生相談室へ出向き担当教員と定期的に相談することができるようになった。個別面談の中では、「授業中に前に出て課題発表を行わなければいけない場面が緊張する」と話していたため、イルボスコを大学の教室に見立てメンバー達の協力を得て発表練習を繰り返す等大学での困難な状況についてロールプレイを行い、その中で対処方法を学習するとともに、慣れない他者との会話の実践の場として学生とのコミュニケーションを繰り返し行った。家族面接の中で、本人が大学生活を順調に送れるようになっていることから、母親が抱く本人の将来への不安が少なくなり、本人への状況確認の連絡も減少した。その結果母親が仕事を再開していたため、母親へは本人と適切な距離を保てていることをフィードバックした。

<アセスメント結果（開始時から利用 15 か月時点での変化）>

PANSS 上の精神症状、Fluency Test、Letter Cancelation Test をはじめとした各種認知機能検査上の認知機能、WHO-QOL 上の主観的 QOL の改善を認めた。また、SFS 総得点において社会機能の著明な改善を認め、中でも「友人と会う」、「居酒屋にいく」、「旅行に行く」等の得点が上がり、友人数が 0 から 15 名へと大幅に増加し、対人交流や行動の範囲が拡大している様子がみられた。イルボスコの集団内で協力して物事を行う機会が増え、その中で様々な役割を得て達成することができ、多くの成功体験を積み重ねることができ、本人もその効果を実感できていた。「自分は誰かの役に立つ」という感覚が育ち、自己効力感の向上につながっていると考えられた。少々の困難であれば立ち向かえるようになる等ストレス対処技能の向上も認められ、悪口を言われる等の幻聴に対しても適切に対処し、休まず通学を継続している。継続した通学が可能になったことで大学生として社会とのつながりを持ち、その後も大学のみでなく、広く社会という集団に所属できている。今後は大学での交友関係の構築、就職等へ向けた将来への自発的な意思決定が課題である。

Ⅶ. イルボスコの成果

イルボスコ開設より 2014 年 9 月 30 日時点の約 7 年間で 193 名の利用者が登録され、登録者の平均年齢は 21.1 歳、対象者の 138 名が FES、55 名が ARMS であった。一日平均利用者数は約 16 名である。FES の DUP 平均値は 10.1 ヶ月、中央値は 2.0 ヶ月であった。活動成果の指標として、イルボスコ利用者の中で、登録期間中に本人が希望する形で社会参加可能となった者の割合を Re-start Rate と定義し、68.2%であった。またイルボスコ利用者の中で、登録期間中に 3 ヶ月以上利用途絶し、かつ社会的転帰が不良の者の割合を Drop-out Rate と定義しているが、その数値は 14.1%であった。

Ⅷ. イルボスコの取り組みにおける今後の展望と課題

近年、神経認知機能と心理社会機能の関連がより詳細に検討される中、社会行動や社会機能に対してそれぞれ独立した関係をもつ可能性がある認知機能として「社会認知」が注目され、治療の標的とした認知機能トレーニングが行われるようになり、社会認知ならびに対人関係のトレーニング（Social Cognition and Interaction Training, SCIT）の効果が報告されている[31]。また、神経認知機能が心理社会機能へ与える作用を媒介する要素として、特に心理社会的機能を高める要素として内発的動機付けの重要性が報告されている[35]。今後、若年者や発症早期段階に向けたアプローチとして、「社会的認知の障害」や「内発的動機付けの向上」を焦点に当てたプログラムを取り入れていく必要があると考えられる。

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A longitudinal study investigating sub-threshold symptoms and white matter changes in individuals with an 'at risk mental state' (ARMS)

Naoyuki Katagiri [a,b], Christos Pantelis [b], Takahiro Nemoto [a,*], Andrew Zalesky [b,c], Masaaki Hori [d], Keigo Shimoji [d,e], Junichi Saito [a], Shinya Ito [f], Dominic B. Dwyer [b], Issei Fukunaga [d], Keiko Morita [a], Naohisa Tsujino [a], Taiju Yamaguchi [a], Nobuyuki Shiraga [g], Shigeki Aoki [d], Masafumi Mizuno [a]

[a] Department of Neuropsychiatry, Toho University School of Medicine, Tokyo, Japan
[b] Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Parkville, Melbourne, Australia
[c] Melbourne School of Engineering, The University of Melbourne, Melbourne, Australia
[d] Department of Radiology, Juntendo University Graduate School of Medicine, Tokyo, Japan
[e] Department of Diagnostic Radiology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan
[f] Department of Social Medicine, Toho University School of Medicine, Tokyo, Japan
[g] Department of Radiology, Toho University School of Medicine, Tokyo, Japan

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ABSTRACT

Background: Evidence supports disruption in white matter (WM) connectivity in established schizophrenia, however, it is unclear when these abnormalities occur during the course of illness and if they are progressive. Here we investigated whether WM abnormalities predate illness onset by examining a group of individuals with an 'at risk mental state' (ARMS) and assess whether there is evidence of progressive change. We hypothesized that WM abnormalities are associated with symptom change.

Methods: Sixteen healthy controls and 41 ARMS subjects at baseline underwent Diffusion Tensor Imaging (DTI). Sub-threshold positive symptoms were measured using the Scale of Prodromal Symptoms (SOPS). Imaging and symptoms were re-administered in the ARMS group after one year (52 weeks). Fractional anisotropy (FA) value differences between ARMS and control groups at baseline were localized using the method of Tract-Based Spatial Statistics (TBSS).

Results: At baseline, FA was significantly reduced in a sub-region of the corpus callosum (CC) in the ARMS group as a whole compared to controls. This reduction was also found in the 34 individuals who did not transition (ARMS-N) during the one-year follow-up. However, the ARMS-N group showed a significant improvement in sub-threshold positive symptoms at follow-up, which was correlated with an increase in FA in the same CC region ($r = -0.664$, $p < 0.001$).

Discussion: There was a significant FA reduction in the CC in individuals at high risk for psychosis regardless of transition status at one year. This suggests that WM abnormalities in the CC may represent a biological vulnerability to psychosis. Improvement in sub-threshold positive symptoms was associated with improvement in measures of WM integrity in the CC. This may suggest that neurobiological 'resilience' is associated with improved outcomes, although this notion requires future study.

1. Introduction

Many studies have revealed that multiple brain regions are implicated in schizophrenia (Shenton et al., 2001). It is postulated that these abnormalities reflect dysfunction of neural connectivity consistent with the disconnection hypothesis of schizophrenia (Friston, 1998). Recently, it has been possible to directly examine the disconnection hypothesis by assessing white matter (WM) connectivity using diffusion tensor imaging (DTI) (Zalesky et al., 2011). A meta-analysis of DTI studies in schizophrenia by Bora et al. (2011) identified significant fractional anisotropy value (FA) reductions in the genu of the corpus callosum, anterior cingulate/medial frontal WM and the anterior limb of the internal capsule and the external capsule/corona radiata. The regions presented in this meta-analysis were largely consistent with abnormalities proposed to be involved in schizophrenia (Crow, 1998; Andreasen, 1999). DTI studies have also identified relationships between FA and various psychiatric symptoms, including positive symptoms, negative symptoms and hallucinations as well as cognitive deficits (for review: Walterfang et al., 2011).

* Corresponding author at: Department of Neuropsychiatry, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, 143-8541 Tokyo, Japan. Tel.: +81 3 3762 4151; fax: +81 3 5471 5774.
E-mail address: takahiro.nemoto@med.toho-u.ac.jp (T. Nemoto).

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However, whether these widespread WM impairments identified with DTI predated the onset of psychotic symptoms or developed over the course of the illness progressively remains unclear (Yung and McGorry, 1996; Pantelis et al., 2003), although this is suggested by progressive WM volumetric changes in UHR individuals converting to psychosis (Walterfang et al., 2008). In a longitudinal DTI study of subjects with 'at risk mental states' (ARMS), Peters et al. (2010) found no baseline FA differences in any brain region between those ARMS patients developing psychosis (ARMS-P) compared with those not developing psychosis (ARMS-N). In contrast, Bloemen et al. (2010) reported that ARMS-P had lower baseline FA in the putamen and in the superior temporal gyrus compared to the ARMS-N. Further, in this study, positive symptom scores in ARMS-P subjects were negatively correlated with FA in the middle temporal lobe, while for the whole ARMS group (ARMS-W) positive symptoms negatively correlated with FA in the right superior temporal lobe. In a previous study, we found a negative correlation between change in FA in the genu of the corpus callosum and change in negative symptoms in ARMS-W during the 52-week study period (Saito et al., in submission). These reports suggest that relationships between symptoms and FA may be relevant to all patients with ARMS, rather than only apparent in those who transition to psychosis.

While transition to psychosis is defined by the expression of prominent positive symptoms, sub-threshold psychotic symptoms gradually develop before onset of psychosis and this increasing severity may be associated with progressive changes in multiple brain regions (Pantelis et al., 2005). To date, no longitudinal DTI studies have examined the relationship of sub-threshold positive symptom changes to WM changes. Further, although, the positive symptoms of almost 80% of ARMS subjects do not exceed the threshold for psychosis and usually recover during the follow-up period, no DTI studies have examined the relationship between recovery of sub-threshold symptoms and the WM changes of these so-called "false positives".

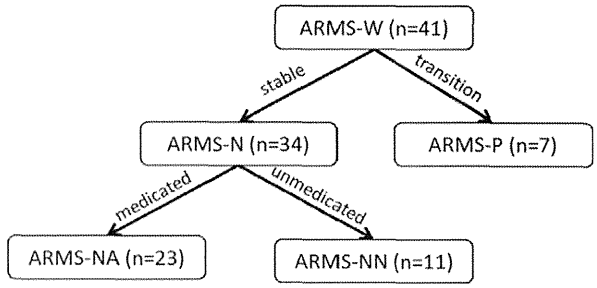
We hypothesized that the severity of sub-threshold positive symptoms that emerge in ARMS subjects is associated with reduction of WM integrity. To elucidate the relationship between sub-threshold positive symptoms and WM integrity in ARMS subjects, we investigated the relationship between cross sectional and longitudinal FA and sub-threshold positive symptoms in ARMS subjects followed for one year.

2. Method

2.1. Participants

The ARMS individuals were recruited at the Toho University Omori Medical Center (baseline). Experienced psychiatrists diagnosed participants as having ARMS using the Structured Interview for Prodromal Syndrome (SIPS) (Miller et al., 2003) at the time of the first consultation. Individuals with clearly diagnosed brain disease or substance dependence were excluded. The ARMS-W group was treated at the "Youth Clinic" and at the "Il Bosco" day-care center that was established for persons with early psychosis (Mizuno et al., 2009; Nemoto et al., 2012). Participants showing severe deterioration of clinical symptoms received antipsychotics even in the absence of apparent positive symptoms (Yung et al., 2007). Transition to psychosis during the follow-up period was defined using the SIPS. After a 52-week follow-up period, the ARMS-W group was divided into ARMS-P and ARMS-N. To investigate the influence of antipsychotics on the ARMS-N group, we further divided ARMS-N subjects into those who were not prescribed antipsychotics (ARMS-NN) and those treated with antipsychotics (ARMS-NA) (Fig. 1). The mean dosage of antipsychotics at baseline and 52 weeks was expressed as milligram equivalents of chlorpromazine (Woods, 2003) and dosage was $\log_{10}$ transformed to reduce skewness (CPZeq-log).

Healthy control subjects were recruited from independent sources in the community and were interviewed in detail by experienced psychiatrists. These individuals had no current psychiatric disorder and no history of psychiatric illness, head trauma, neurological illness, serious medical illness or substance dependence. Written informed consent was obtained from all the participants after the study had been explained in full. This study was approved by the Ethics Committee of the Toho University School of Medicine.



ARMS-W: overall group of ARMS subjects; ARMS-P: ARMS subjects who developed psychosis during the 1-year follow-up period; ARMS-N:ARMS subjects who did not develop psychosis during the 1-year follow-up period; ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period.

Fig. 1. Flow chart outlining of participants. ARMS-W: overall group of ARMS subjects; ARMS-P: ARMS subjects who developed psychosis during the 1-year follow-up period; ARMS-N:ARMS subjects who did not develop psychosis during the 1-year follow-up period; ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period.

2.2. Scaling of the severity of sub-threshold positive symptoms

The Scale of Prodromal Symptoms (SOPS) (Miller et al., 2003) is contained within the SIPS. The SOPS has been designed to define and diagnose the psychosis prodrome, to characterize the symptoms and their severity and, importantly, to assess change longitudinally. The SOPS is a 19-item scale designed to measure the severity of prodromal symptoms and changes over time. The SOPS contains four subscales for Positive, Negative, Disorganization, and General symptoms. In this study, sub-threshold positive symptom severity of ARMS subjects was calculated as the sum of the five SOPS positive items (POS) at baseline and at 52 weeks. For longitudinal analysis, the one-year change in POS (ΔPOS) was calculated by subtracting POS score at baseline from the score at 52 weeks.

2.3. Image acquisition

The ARMS subjects and controls underwent MRI scans (EXCELART Vantage, XGV 1.5T; Toshiba Medical Systems, Tokyo, Japan) with a five-channel head coil at baseline; DTI images were acquired by using a single-shot spin-echo echo-planar sequence in 30 axial sections. The whole brain diffusion-weighted images were recorded along 6 gradient directions using a b-value of 1000 s/mm^2 together with unweighted ($b = 0$) images. For each image, we used the following parameters: field of view = 260 × 260 mm^2; matrix size 128 × 128; voxel resolution 1.02 × 1.02 × 5 mm^3; TE = 100 ms; TR = 7,668 ms; number of signal average 3. After 52 weeks from baseline scan, ARMS subjects underwent a second scan using the same instrument and same method.

Although some of subjects underwent SIPS and MRI repeatedly during the follow-up period, to analyze strictly, we adopted the SIPS and MRI data at 52 weeks for each subject.

2.4. Image processing

In the previous study, we measured the FA values, using Tract Specific Analysis (TSA), of each of the three CC sub-regions that were

manually segmented based on brain anatomy (Saito et al., in submission). However, in this study, using Tract-Based Spatial Statistics analysis (TBSS), we analyzed the precise difference in FA values of cerebral white matter between ARMS-W and controls (Smith et al., 2006). Briefly, correction for the effects of head movement and eddy currents was performed. A brain mask was created by using one of the b = 0 (no diffusion weighted) images. A diffusion tensor was then fitted to each voxel comprising the mask and FA images were computed. Each image was aligned to a common space (FMRIB58-FA standard-space image) using the nonlinear registration tool FNIRT which uses a *b*-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton.

Group comparisons between ARMS-W and controls were carried out using t-tests. These were computed using the randomize function implemented in FSL, and implementing the recently developed threshold-free cluster-enhancement method for proper statistical inference of spatially distributed patterns. A p-value of <0.05 was regarded as significant. Family-wise error was used to correct for multiple comparisons. In this way, significant regions of interest (ROIs) were identified and delineated for further analysis, as below.

2.5. Quantification of FA of significant ROIs

To analyze the longitudinal FA differences between the various subgroups at baseline and 52 weeks, we specifically investigated FA in the ROIs identified in the previous step. Using a custom MATLAB (www.mathworks.com.jp) script, the average of the FA across all the voxels comprising the significant regions identified with TBSS was computed. For longitudinal analysis, the one-year changes in FA (ΔFA) of each group were calculated by subtracting the FA values at baseline from the values at 52 weeks.

2.6. Statistical analysis

Data were analyzed using SPSS version 20 (www.spss.com). We first compared differences in baseline POS scores and ROI FA values between controls, ARMS-NN, ARMS-NA and ARMS-P using ANOVA. Post-hoc tests were examined using Tukey HSD. We also examined the longitudinal changes in FA and POS scores respectively between ARMS-NN and ARMS-NA between baseline and one year, using repeated measures ANOVA that included a between-group factor (ARMS-N subgroups) and a within-subject factor (baseline and 52 weeks).

To investigate the longitudinal relationship between FA changes and POS changes during follow-up, we analyzed the correlation between ΔFA and ΔPOS in the ARMS subgroups.

Regression analysis was used to investigate factors that influenced POS changes over the follow-up in the ARMS-N subgroups. The dependent factor was ΔPOS. The regressor of interest was ΔFA. For ARMS-NN, age, sex and ΔFA were included as regressors. For ARMS-NA, age, sex, ΔFA and the mean dosage of antipsychotics during the one-year follow-up period were included as regressors. The mean dosage of antipsychotics during the one-year follow-up period was calculated as the mean value of antipsychotic dosage (milligram equivalents of chlorpromazine) at the two time points (baseline and 52 weeks) and mean dosage for each person was $\log_{10}$ transformed to reduce skewness (CPZeq-mean-log).

3. Results

3.1. Demographic and characteristics of the groups

Participants were sixteen controls and 41 ARMS-W. Seven of 41 (17.1%) subjects transitioned to psychosis during the one-year follow-up. Among these 7 ARMS-P subjects 2 subjects did not undergo the SIPS and 2 subjects did not undergo MRI at follow-up (i.e. only four underwent both SIPS and MRI at both baseline and 52 weeks). Thus, this group was not included in the longitudinal analysis (i.e. analyses were limited to the ARMS-N subgroups).

Among 34 ARMS-N, 23 subjects had been prescribed antipsychotics (ARMS-NA) during the follow-up. Of 23 ARMS-NA subjects followed up at 52 weeks, 5 subjects did not undergo SIPS and 1 subject did not undergo MRI, and among 11 ARMS-NN subjects followed up, 2 subjects did not complete SIPS. The demographic characteristics of the groups are shown in Table 1.

There were no significant group differences in dose of medication between ARMS-NA and ARMS-P at baseline ($t(28) = -1.361$, $p = 0.18$). Within ARMS-NA, there was no significant difference in dose of medication between baseline and 52 weeks ($t(22) = -0.727$, $p = 0.48$). All ARMS-P subjects received antipsychotics at baseline because they had shown evidence of clinical deterioration, even though positive symptoms were not prominent. Further, while these subjects converted to psychosis during the one-year follow-up period with increased dose of antipsychotics during the acute phase, all patients had been treated at the "Youth Clinic" and the "Il Bosco" and reached remission before 52 weeks. Consequently, the mean dose of antipsychotics was reduced again by 52 weeks.

3.2. POS score of ARMS subgroups

Assessment at baseline did not identify any significant differences in POS between ARMS-NN, ARMS-NA and ARMS-P at baseline ($F(2,36) = 0.709$, $p = 0.50$). Repeated measures analysis examining changes over time (excluding the ARMS-P because of low numbers) indicated that there was no significant main effect of group ($F(1,25) = 0.064$, $p = 0.80$) between ARMS-NN and ARMS-NA. However, there was a significant effect of time for POS score ($F(1,25) = 19.001$, $p < 0.001$) and a significant time × group interaction ($F(1,25) = 4.985$ $p = 0.035$), with greater POS reduction observed in the ARMS-NA group.

3.3. FA differences between the ARMS group and controls at baseline

Comparing FA between groups, significant differences were found between the ARMS-W and controls at baseline using TBSS, in one cluster involving part of the genu and body of the corpus callosum (CC) (confirmed with JHU ICBM-DTI-81 WM Labels) (Fig. 2).

3.4. Group differences in FA at baseline

The region identified in Fig. 2, where the significant FA reduction was detected in the ARMS-W compared to controls was defined as the ROI.

At baseline the FA in the ROI differed significantly across groups (controls, 0.47 ± 0.04; ARMS-NN, 0.39 ± 0.05; ARMS-NA, 0.40 ± 0.07; ARMS-P, 0.43 ± 0.06); ($F(3,53) = 5.701$, $p = 0.002$). Post-hoc tests revealed significant differences in FA between controls and ARMS-NN ($p = 0.004$) and between controls and ARMS-NA ($p = 0.005$) (Fig. 3).

3.5. Longitudinal relationship between FA changes and changes in POS in ARMS-N subgroups

For comparison of FA between ARMS-NN and ARMS-NA, there was no significant effect of group ($F(1,31) = 0.517$, $p = 0.48$), time ($F(1,31) = 0.339$ $p = 0.567$) or time × group interaction ($F(1,31) = 1.000$, $p = 0.33$).

Nine ARMS-NN, 17 ARMS-NA and 4 ARMS-P subjects underwent both MRI and SOPS at baseline and 52 weeks. There was a significant correlation between ΔFA and ΔPOS between baseline and one year for each of the ARMS subgroups (ARMS-W, $n = 30$, $r = -0.568$, $p =$

Table 1
Demographic data, scores for sub-threshold positive symptoms (POS), and fractional anisotropy values (FA).

	Baseline					52 weeks			
	Control	ARMS-NN	ARMS-NA	ARMS-P	p	ARMS-NN	ARMS-NA	ARMS-P	p
Participants (male/female)	n = 16 (8/8)	n = 11 (3/8)	n = 23 (6/17)	n = 7 (1/6)	p = 0.273	n = 11 (3/8)	n = 23 (6/17)	n = 7 (1/6)	p = 0.789
Age at baseline and 52 weeks (years)	23.19 (2.86)	24.18 (7.88)	23.35 (6.49)	20.71 (5.53)	p = 0.673	25.09 (7.80)	24.48 (6.45)	21.20 (5.26)	p = 0.549
Subject underwent SOPS (male/female)	–	n = 11 (3/8)	n = 21 (4/17)	n = 7 (1/6)	p = 0.778	n = 9 (2/7)	n = 18 (4/14)	n = 5 (1/4)	p = 0.994
POS score at baseline and 52 weeks	–	17.36 (3.26)	19.05 (4.18)	19.14 (4.67)	p = 0.499	15.22 (5.09)	13.22 (4.953)	16.80 (4.09)	p = 0.301
Subject underwent DTI (male/female)	n = 16 (8/8)	n = 11 (3/8)	n = 23 (6/17)	n = 7 (1/6)	p = 0.273	n = 11 (3/8)	n = 22 (6/16)	n = 5 (1/4)	p = 0.942
FA value in ROI at baseline and 52 weeks	0.47 (0.04)	0.39 (0.05)	0.40 (0.07)	0.43 (0.06)	p = 0.002**	0.38 (0.04)	0.40 (0.04)	0.43 (0.06)	p = 0.128
Subject underwent DTI and SOPS at baseline and 52 weeks (male/female)	–	n = 9 (2/7)	n = 17 (4/13)	n = 4 (1/3)	p = 0.994	n = 9 (2/7)	n = 17 (4/13)	n = 4 (1/3)	p = 0.994
Dose of CPZeq-log	–	0	1.75 (0.62)	2.06 (0.39)	–	0	1.80 (0.64)	2.37 (0.32)	–

ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the 1-year follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; ARMS-P:ARMS subjects who developed psychosis during the follow-up period.
* $p < 0.05$.
** $p < 0.01$.

0.001; ARMS-N, n = 26, r = −0.664, p < 0.001; ARMS-NN, n = 9, r = −0.776, p = 0.014; ARMS-NA, n = 17, r = −0.586, p = 0.013). However, the correlation was not significant in the ARMS-P group (n = 4, r = 0.139, p = 0.86) (Fig. 4).

The determinants of ΔPOS were examined further using regression to assess the effects of FA, age, gender and mean dosage of antipsychotics during the one-year follow-up. Only ΔFA significantly correlated with ΔPOS for both subgroups (ARMS-NN p = 0.03; ARMS-NA: p = 0.004). Mean antipsychotic dose was not associated with ΔPOS in the ARMS-NA group (ARMS-NA: p = 0.96) (Table 2).

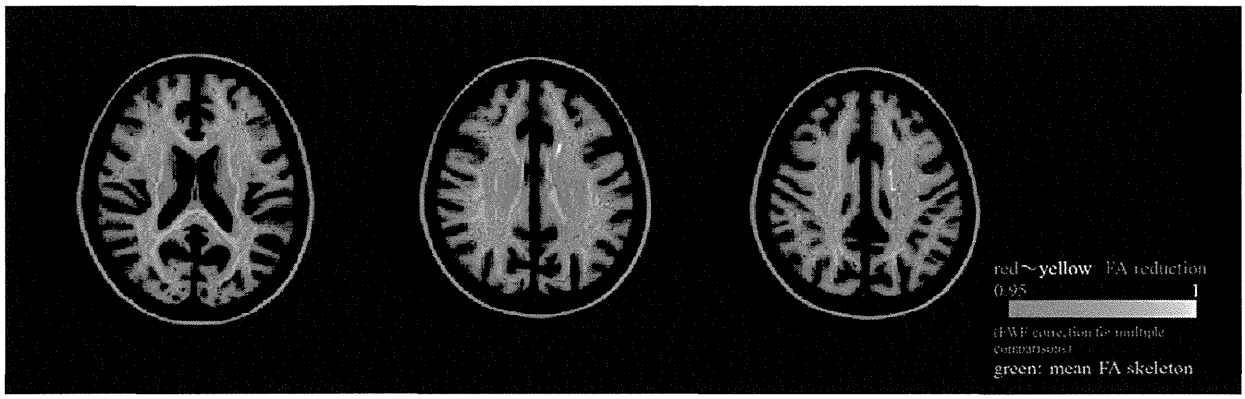
4. Discussion

In this study we examined WM integrity in prepsychotic individuals considered at-risk for psychosis.

In the cross sectional analysis, FA values in the CC for the ARMS-P group was intermediate relative to controls and ARMS-N group (Fig. 3). While this result is not in accordance with our hypothesis that severity of symptoms would be associated with reduction of WM integrity or previous findings that reported FA reductions in the left CC of ARMS-P group (Carletti et al., 2012), our sample of converters was small. However, some recent studies suggest that FA reductions in the brain of schizophrenia patients were inhomogeneous across different sub-regions of the CC. Thus, Schneiderman et al., (2009) reported that although the DTI index was lower in most regions of CC, it was higher in the right body and left anterior portion of the genu in male schizophrenia patients compared to controls.

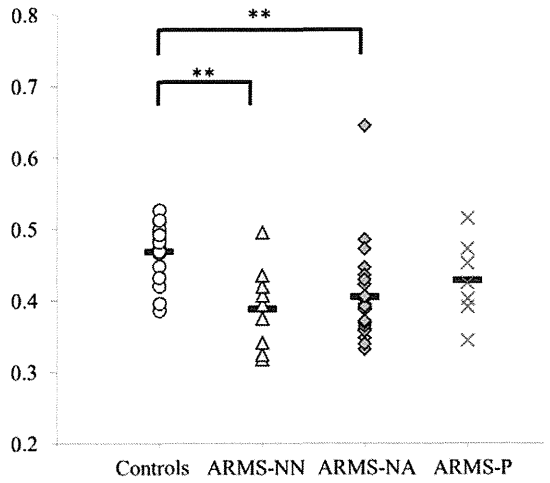
In contrast, in the ARMS-N group there was a significant FA reduction in the CC compared to healthy controls at baseline. These results raise the possibility that sub-threshold psychotic symptoms observed in ARMS-N are associated with potentially deleterious biological differences affecting white matter integrity.

In the longitudinal analysis, only seven individuals converted to psychosis (ARMS-P) during the follow-up period and because only 4 subjects underwent both MRI and SOPS at follow-up, our main results relate to those who did not convert to psychosis. Interestingly, this ARMS-N group showed a significant improvement in sub-threshold positive symptoms (POS) during one-year follow-up and this improvement was associated with increased FA. This finding was not explained by potential confounders including age and gender. Further, analysis of the ARMS-N subjects (including medicated and antipsychotic-naïve) identified the same relationship between POS and FA. While these findings suggest that this change was not explained by use of antipsychotics, further study is needed to increase the number of unmedicated subjects. These results indicate that improvement in the severity of sub-threshold psychotic symptoms was associated with improved indices of white matter integrity in a sub-region of the left CC.



ARMS-W: overall group of ARMS subjects; Image is radiologically oriented (participant's left is to the right) ; p-value <0.05 was regarded as significant (after family-wise error correction for multiple comparison).

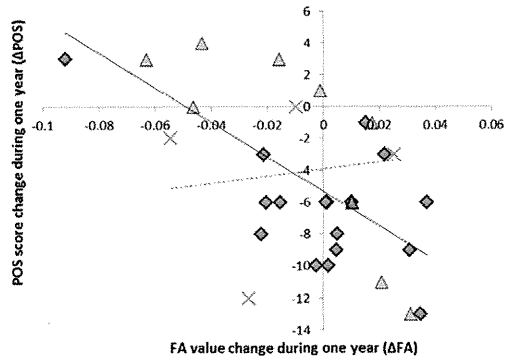
Fig. 2. Significant FA differences between ARMS-W group and controls. ARMS-W: overall group of ARMS subjects; Image is radiologically oriented (participant's left is to the right) ; p-value < 0.05 was regarded as significant (after family-wise error correction for multiple comparison).



ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; ARMS-P: ARMS subjects who developed psychosis during the follow-up period. *P <0.05; **P < 0.01.

Fig. 3. Mean FA value of controls and ARMS subgroups at baseline. ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; ARMS-P: ARMS subjects who developed psychosis during the follow-up period. *P < 0.05; **P < 0.01.

We found that improvements in WM measures were accompanied by improvement in such symptoms, suggesting a dynamic process that may be relevant to the onset of disorder. While our sample of ARMS-P was inadequate to examine this further, an intriguing hypothesis is that improvement in white matter over time reduces the risk for developing psychosis. This may imply neurobiological resilience in a subgroup of young people deemed at risk for psychosis (see: Pantelis and Bartholomeusz, 2014).



Green triangles: scatter of ARMS-NN; Blue diamonds: scatter of ARMS-NA; Red X: scatter of ARMS-P. Red broken line: regression line of ARMS-P; Black solid line: regression line of ARMS-N. ΔPOS: one-year change in POS; ΔFA: one-year change in FA; ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; ARMS-P: ARMS subjects who developed psychosis during the follow-up period.

Fig. 4. Correlations between ΔFA and ΔPOS for ARMS subgroups. Green triangles: scatter of ARMS-NN; Blue diamonds: scatter of ARMS-NA; Red X: scatter of ARMS-P. Red broken line: regression line of ARMS-P; Black solid line: regression line of ARMS-N. ΔPOS: one-year change in POS; ΔFA: one-year change in FA; ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; ARMS-P: ARMS subjects who developed psychosis during the follow-up period.

The CC is the largest commissure in the human brain, connecting neocortical regions of the two hemispheres. This includes the left and right frontal areas, associated with specific higher cognitive functions (de Lacoste et al., 1985). Further, the normal human brain is characterized by a pattern of gross anatomical asymmetry, which has been associated with the processing of language (Cook, 2002). Individuals with schizophrenia show a loss of the normal asymmetry in regions such as superior temporal gyrus relevant to language (e.g., Crow et al., 2007). Asymmetry in schizophrenia is also observed in anterior cingulate region close to the CC (Yücel et al., 2002), which has been associated with impairments in executive function (Fornito et al., 2006). Crow (1998) has proposed a translocation misconnection syndrome based on such evidence together with evidence for asymmetry in the CC (Highley et al., 1999), a finding that is consistent with our findings implicating left CC. Impairment of CC in schizophrenia had been consistently reported in neuroimaging studies (e.g. Walterfang et al., 2006), including the meta-analysis of schizophrenia DTI studies finding FA reductions in this region (Patel et al., 2011). Similar to our study, Carletti et al. (2012) reported reduction of DTI indices in the left CC of ARMS individuals, which were intermediate between first episode schizophrenia and controls. Additionally, Knochel et al. (2012) reported volume and FA reductions of CC in schizophrenia as well as first-degree relatives suggesting a role for genetic influences. This may also suggest that such measures represent potential endophenotypic markers for schizophrenia.

Our findings indicate that the increase of FA in CC was associated with improvement or recovery of POS rather than antipsychotics in ARMS-N group. There is already some evidence of relationships between psychiatric symptoms and the impairment of CC in schizophrenia (Bleich-Cohen et al., 2012; Nakamura et al., 2012; Serpa et al., 2012). These reports support our findings in ARMS, suggesting that changes in psychiatric symptom severity are associated with changes of CC WM integrity.

Taken together with the consistent reports of impairment of frontal CC in the ARMS as well as schizophrenia, our results of FA reduction in anterior CC in the ARMS group are in accordance with previous studies. However, to our knowledge, this is the first study that reports FA reduction in ARMS that have not made the transition to psychosis, so-called "false positive" cases; and the first study to report FA changes over time in such a group. These results raise the possibility that the "false positives" do not simply express sub-threshold psychotic symptoms, but also manifest neurobiological risk for developing psychosis and that our findings of improvement in FA over a 12-month period relate to 'protective' factors or 'neurobiological resilience' (Pantelis and Bartholomeusz, 2014).

On the other hand, theoretically, true positives (those making the transition) will be outnumbered by "false positives". However, there is the possibility of "false false positives", that is those who would have made the transition to psychotic disorder had it not been for some intervention or change in circumstances (Yung et al., 2007). This is particularly the case in our study, as all ARMS patients underwent various therapies including a proportion receiving medication. However, we have demonstrated that a positive change in FA was associated with fewer symptoms, suggesting that neurobiological vulnerability can be modified.

Takeuchi et al. (2010) reported that working memory training correlated with increased FA in the WM regions adjacent to the intraparietal sulcus and the body of the CC after training in healthy people. Penades et al. (2013) reported that schizophrenia patients who underwent cognitive remediation therapy showed increase of FA in the genu of the CC. Such studies suggest that changes at the earliest stages of psychosis and pre-psychosis are dynamic and changeable, potentially reflecting plasticity. Importantly, our findings are indicative of positive neurobiological outcomes that may be associated with amelioration of

Table 2
Results of regression analyses for ΔPOS of ARMS-N subgroups.

	ARMS-NN				ARMS-NA			
Regressor of ΔPOS	β	t	p	(95% CI)	β	t	p	(95% CI)
age	−0.248	−0.932	0.394	−0.882 to 0.384	−0.452	−1.889	0.083	−0.596 to 0.042
sex	−0.441	−1.756	0.139	−15.509 to 2.918	0.431	1.802	0.097	−0.782 to 8.252
ΔFA	−0.714	−3.012	0.030	−245.837 to −19.433*	−0.791	−3.548	0.004	−160.759 to −38.430**
CPZeq-mean-log	-	-	-		0.010	0.046	0.964	−4.718 to 4.922

ARMS-N:ARMS subjects who did not develop psychosis during the 1-year follow-up period; ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; ΔPOS: one-year change in POS; ΔFA: one-year change in FA.
* $p < 0.05$.
** $p < 0.01$.

symptoms and possibly illness prevention. Further work should explore ways to reduce such neurobiological vulnerability, including measures of WM integrity.

We acknowledge some limitations to our study. First, the risk of Type II errors should be considered in view of the relatively small sample sizes, particularly for the ARMS-P. Second, while TBSS has been widely used to identify focal between-group differences in FA, this approach is associated with several limitations, including disregard for potential effects outside of the 'skeleton' and evidence showing the tract-specificity of the skeleton projection step may be low for some fiber geometries (Zalesky, 2011; Keihaninejad et al., 2012). Despite these methodological considerations, TBSS is currently still considered the leading technique for voxel-wise diffusion imaging analysis as many alternative approaches are far less reproducible and may have similar problems (Bach et al., 2014).

Third, although the effect of gender differences was not significant in our study, we did not specifically design the study to examine the role of sex differences (Crow et al., 2013). Savadjiev et al., (2014), in their study of schizophrenia patients, reported a significant diagnosis by sex interaction of DTI indices in the left anterior CC. Further, they reported a difference in the correlation between the severity of patients' negative symptoms and DTI indices in the left anterior CC in both sexes. These results coincide with previous studies suggesting that the structural change underlying the continuum of psychosis relates to the interaction of laterality and sex (Bora et al., 2012; Lagopoulos et al., 2013). Further work is required to clarify the effects of gender, laterality or clinical subtypes on FA change on CC.

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Contributors

Naoyuki Katagiri and Masafumi Mizuno designed the study and wrote the protocol. Junichi Saito, Naohisa Tsujino, Taiju Yamaguchi, Shinya Ito, Nobuyuki Shiraga and Shigeki Aoki were involved at the conceptualization level of the project. Keiko Morita and Naoyuki Katagiri collected the data. Masaaki Hori, Keigo Shimoji, Issei Fukunaga, contribute to image processing. Naoyuki Katagiri, Takahiro Nemoto, Andrew Zalesky, Dominic Dwyer and Christos Pantelis analyzed the data. Naoyuki Katagiri wrote the draft of this manuscript. Masafumi Mizuno, Christos Pantelis and Takahiro Nemoto contributed to the writing and revision of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Long-term course of cognitive function in chronically hospitalized patients with schizophrenia transitioning to community-based living

Takahiro Nemoto [a,*], Hidehito Niimura [b], Yonosuke Ryu [b], Kei Sakuma [c], Masafumi Mizuno [a]

[a] Department of Neuropsychiatry, Toho University School of Medicine, Tokyo, Japan
[b] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan
[c] Asaka Hospital, Koriyama, Fukushima, Japan

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ABSTRACT

Schizophrenia is associated with impairments in social interactions, and the conditions under which patients live and undergo treatment appear to have an important role in the course of the disease. However, the influences of care settings on the course of cognition remain controversial. The closure of psychiatric hospitals and the transition to community-based living is a golden opportunity to address this issue. The aims of the present study were to examine (1) the longitudinal course of cognition as well as the psychopathology and social functioning of schizophrenia patients who had been chronically hospitalized and then discharged, and (2) the key cognitive predictors of the functional outcome of such patients. Seventy-eight patients were transferred to the community after the closure of a psychiatric hospital. These patients were followed-up for 5 years and underwent annual examinations that included measures of cognition, psychiatric symptoms, and social functioning. Fifty-six patients completed all the assessments. Although consistent improvements were shown in the cognitive domains for attention and memory, the initial improvements in global cognition and processing speed ultimately began to decline. Symptoms and global functioning improved almost consistently over the course of the follow-up period. Stepwise multiple regressions revealed category fluency at baseline predicted social functioning at 5 years. However, this correlation was no longer significant when psychopathological variables were included as predictors. These results suggest that care settings affect the course of cognition, and addressing these conditions may lead to a certain degree of cognitive improvement even among schizophrenia patients who have been chronically institutionalized.

1. Introduction

Schizophrenia is associated with impairments in day-to-day social interactions, and the conditions under which patients live and undergo treatment appear to have an important role in the course of the disease. Regarding the long-term course of cognitive function in patients with schizophrenia, the influences of care settings have been examined mainly by contrasting chronic inpatients and outpatients who are inevitably elderly, although cognition in patients with schizophrenia is thought to be stable over an individual's lifespan. Many of the longitudinal studies on cognition in patients with chronic schizophrenia have been performed by two research groups: one in New York, and the other in San Diego. The New York group has mainly examined cognition in chronically hospitalized patients with schizophrenia based on limited cognitive assessments; this group has demonstrated a cognitive decline after a few years of follow-up in these subjects (Harvey et al., 1999a, 1999b; McGurk et al., 2000). In contrast, the San Diego group has studied cognition in community-dwelling elderly patients using global screening or measures and has reported stable cognitive function over a follow-up period of a few years (Heaton et al., 2001; Palmer et al., 2003; Nayak Savla et al., 2006).

It is difficult to interpret the results of studies in which inpatients and outpatients are directly compared because patients who have a better cognitive performance are more likely to be discharged, and cognitive deficits might serve as selection factors for long-term institutionalization, rather than long-term institutionalization being a cause of cognitive deficits (Abrahamson, 1993). A previous study adopted a longitudinal comparison of the courses of outpatients with schizophrenia who varied in their history of institutionalization to address the question of the influences of care settings on cognitive function (Harvey et al., 2010); however, this study was limited in that the duration during which the participants dwelled within and became adjusted to the community varied. One ideal study design would be a longitudinal comparison of

* Corresponding author at: Department of Neuropsychiatry, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan. Tel.: +81 3 3762 4151; fax: +81 3 5471 5774.
E-mail address: takahiro.nemoto@med.toho-u.ac.jp (T. Nemoto).

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cognitive performance in pairs of schizophrenic patients admitted at the same time and to the same institution, matched for most clinical and cognitive variables, with the exception that one group of patients was continuously institutionalized while the other group was immediately discharged and never or only briefly readmitted (Davidson and Haroutunian, 1995). However, such studies are practically impossible. The closure of psychiatric hospitals and the transition to community-based living seems to be a golden opportunity to address this issue.

A trend toward deinstitutionalization, including the closure or downsizing of large psychiatric hospitals and the establishment of alternative community services, began in the 1950s (Avison and Speechley, 1987), and psychiatric care in the community is common at present and is taken completely for granted by patients with schizophrenia, with comprehensive services having been advanced. A number of reports on the transition to community-based living have been published, and good psychopathology and functional outcomes generally appear to be associated with patients who have been discharged from psychiatric hospitals into the community with the support and care provided by service centers, whereas poor outcomes are associated with a continued inpatient status (Davidson and Haroutunian, 1995).

The course of cognitive impairments in schizophrenia patients during their transition from psychiatric hospitals to the community remains obscure. Trieman et al. (1996) demonstrated that geriatric schizophrenic patients who were discharged from hospital, but not those who remained institutionalized, exhibited preserved levels of cognitive and living function during a 3-year follow-up period. This result could be interpreted as evidence that care settings are causally related to cognitive impairment; however, only one cognitive measure was administered.

The Sasagawa Project, the earliest large-scale project to enable a total transition from a psychiatric hospital to a residential facility in Japan, was established in Koriyama City, Fukushima (Mizuno et al., 2005; Ryu et al., 2006). In this project, 78 chronic patients with schizophrenia were transferred to the community after the closure of a psychiatric hospital. Many of these patients were followed for 5 years and underwent annual examinations that included measures of cognitive function, psychiatric symptoms, and social functioning.

The aims of the present study were to examine (1) the longitudinal course of cognitive function as well as the psychopathology and social functioning of schizophrenia patients who had been chronically hospitalized and then discharged in relation to a change from inpatient to outpatient psychiatric care, and (2) the key cognitive predictors of the functional outcome of such patients.

2. Methods

2.1. Participants

In the Sasagawa Project, 78 Japanese patients with schizophrenia (51 men, 27 women) who had been chronically admitted at the Sasagawa Hospital made preparations to be discharged in 2001 and received psychosocial training for one year based on the Optimal Treatment Project (OTP; Falloon et al., 2004) for their transition to the community. Two trained psychiatrists independently diagnosed the participants using the ICD-10 criteria (World Health Organization, 1993). The mean age of the patients was 54.6 years (SD = 7.2 years), the mean number of years of education was 10.4 years (SD = 1.8 years), the mean age of onset was 23.1 years (SD = 5.7 years), and the mean length of hospitalization was 25.6 years (SD = 10.2 years). All the patients were taking antipsychotic medications (708.3 mg/day chlorpromazine equivalent, SD = 503.2). The subjects had previously been excluded from the study if they had a history of alcohol dependence, substance abuse, or a neurological illness.

The patients were then discharged from the hospital and were transferred to a supported residential facility called the Sasagawa Village immediately after the closure of the hospital at the end of March 2002. Since that time, the patients gradually left the residential facility and completed their move into the neighboring community by 2007, where they now mainly live in group homes and several apartment houses. They attend various programs to enrich their lives including sports, cooking, playing musical instruments, and learning computer skills at a daycare center and a community care center. They also receive regular nursing care visits. Some of them began participating in a job-training program and then earned spending money. As the entrance hall at the residential facility was utilized as a meeting place where local people could get together and many events were held for the community, the patients could naturally keep in contact with people in the neighborhood. In this manner, they were able to resume their own lives and to enjoy a free way of life.

Our institutional review board approved the protocol of the present study. After providing the subjects with a complete description of the study, written informed consent was obtained from every subject. The entire assessment procedure for the Sasagawa Project (Mizuno et al., 2005) and the 2-year outcomes with regard to psychopathology and social functioning (Ryu et al., 2006) have been published elsewhere.

2.2. Measures

Measures of cognition included the Letter Cancellation Test (LCT, number of correct responses; Diller et al., 1974) as a measure of attention, the Digit Span (DS) of the WAIS-R (scores for forward and backward; Wechsler, 1981) as a measure of attention/working memory, the Rey–Osterrieth Complex Figure Test (ROCFT, scores for the immediate and delayed recall trial; Lezak et al., 2004) as a measure of memory, the Word Fluency Test (WFT, scores for letter and category fluency; Benton, 1968; Nemoto et al., 2005) as a measure of executive function, the Trail Making Test Part A (TMTA, required time; Reitan, 1958) as a measure of processing speed, and the Mini-Mental State Examination (MMSE; Folstein et al., 1975) as a measure of global cognition.

The Positive and Negative Syndrome Scale (PANSS; positive symptoms, negative symptoms, and general psychopathology subscales; Kay et al., 1987) were used to assess psychiatric symptoms, and the Social Functioning Scale (SFS, total score; Birchwood et al., 1990; Nemoto et al., 2008) was used to assess social functioning. In addition, the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) was used to measure global functioning (clinical and social combined). Clinical assessments and cognitive tests were administered at baseline and annually for 5 years.

2.3. Data analyses

All the statistical analyses were performed using PASW Statistics 18. A one-way repeated-measures analysis of variance (ANOVA) was used to examine each statistical change in the cognitive, psychopathological, and functional variables, and the Tukey HSD was used on a post-hoc basis. Stepwise multiple regressions were used to examine the predictability of cognition using two functional outcome measures (SFS and GAF). The cognitive domain consisted of the 9 variables described above.

3. Results

3.1. Follow-up

Four patients were re-hospitalized chronically (for over 1 year) because of the exacerbation of their mental illnesses, and 3 patients were hospitalized because of physical illnesses during the follow-up period. Fifty-six patients (71.8%) among the 78 patients completed all the assessments and cognitive tests. The demographic characteristics of these patients at baseline were as follows: 38 men and 18 women; mean age, 54.6 years old (SD = 7.3 years); education, 10.5 years (SD = 2.0 years); the mean duration of illness, 31.5 years (SD =

8.7 years); length of hospitalization, 25.5 years (SD = 9.9 years); medication dose, 710.4 mg/day chlorpromazine equivalent (SD = 530.8).

3.2. Course of cognitive function

A one-way repeated-measures ANOVA test revealed significant differences in some repeated cognitive variables. Significant changes over 5 years were observed for the MMSE results ($F = 2.824$, $df = 5, 275$, $P = 0.032$), LCT ($F = 6.775$, $df = 5, 275$, $P = 0.002$), ROCFT immediate recall ($F = 2.530$, $df = 5, 275$, $P = 0.040$), ROCFT delayed recall ($F = 16.728$, $df = 5, 275$, $P < 0.001$), WFT letter fluency ($F = 7.138$, $df = 5, 275$, $P < 0.001$), WFT category fluency ($F = 2.560$, $df = 5, 275$, $P = 0.042$), and TMTA ($F = 3.109$, $df = 5, 275$, $P = 0.020$). The results are summarized in Table 1. Data for the measures in which significant changes were demonstrated between baseline and each follow-up point using the Tukey HSD post-hoc test are graphically presented in Fig. 1. Although consistent improvement was shown for the LCT and the ROCFT delayed recall, the initial improvement in the MMSE and TMTA began to decline within a few years.

3.3. Course of psychiatric symptoms and social functioning

One-way repeated-measures ANOVA tests revealed significant differences in repeated clinical variables. Significant changes over 5 years were observed for positive symptoms ($F = 8.134$, $df = 5, 275$, $P = 0.001$), negative symptoms ($F = 34.169$, $df = 5, 275$, $P < 0.001$), and the general psychopathology subscales of the PANSS ($F = 38.310$, $df = 5, 275$, $P < 0.001$) and the GAF ($F = 17.841$, $df = 5, 275$, $P < 0.001$). The results are summarized in Table 2. Data for the measures in which significant changes were demonstrated between baseline and each follow-up point using the Tukey HSD post-hoc test are graphically presented in Fig. 2.

3.4. Predictor of 5-year functional outcome

A stepwise multiple regression analysis using cognitive variables at baseline and demographic variables (age and duration of illness) as independent variables was generated for each functional outcome variable at 5 years to identify predictors that were closely associated with the future functional outcome.

The model for the SFS was significant ($F = 7.099$, $df = 1, 54$, $P = 0.010$; adjusted $R^2 = 0.100$), with the category fluency score identified as a statistically significant predictor (Beta = 0.341, $P = 0.010$). The model for the GAF was also significant ($F = 9.189$, $df = 1, 54$, $P = 0.004$; adjusted $R^2 = 0.130$) and included the category fluency score as a significant predictor (Beta = 0.381, $P = 0.004$). These results indicated that a higher semantic fluency ability at baseline contributed to a higher level of social functioning at 5 years. As a second step, psychopathological variables (3 subscales of the PANSS) were also used as independent variables in addition to the cognitive and demographic variables. The model for the SFS was significant ($F = 34.182$, $df = 1, 54$, $P < 0.001$; adjusted $R^2 = 0.376$), with the negative symptoms of the PANSS identified as a statistically significant predictor (Beta = −0.623, $P < 0.001$). The model for the GAF was also significant ($F = 11.649$, $df = 2, 53$, $P < 0.001$; adjusted $R^2 = 0.279$) and included both the positive symptoms (Beta = −0.394, $P = 0.002$) and the negative symptoms (Beta = −0.293, $P = 0.017$) as significant predictors. When including psychopathological variables as independent variables, the category fluency score was no longer a significant predictor of functional outcomes.

4. Discussion

4.1. Course of cognitive function

The results suggested that even patients with schizophrenia who have been chronically hospitalized could show a certain degree of improvement in some cognitive deficits after dwelling within the community following their discharge from hospital, although the changes in the variables were relatively small. Cognitive deficits in patients with schizophrenia are generally considered to be relatively stable over long periods of time (Rund, 1998). Heaton et al. (2001) described the stability of cognitive function over an average follow-up period of 3 years among community-dwelling subjects, while cognition has typically been shown to decline in institutionalized patients. Trieman et al. (1996) also reported a preserved cognitive function during a 3-year follow-up period in outpatients. A review described middle-aged and elderly institutionalized patients with schizophrenia as showing a decline in gross measures of cognitive function (Kurtz, 2005). To the best of our knowledge, no previous report has demonstrated a change for the better in cognitive function after a transition to the community among chronically hospitalized patients with schizophrenia. Cross-sectional reports suggest that elderly patients with schizophrenia have mostly consistent impairments in executive function and verbal fluency, although impairments have less consistently been observed for memory, attention, and working memory (Rajji and Mulsant, 2008). The present results suggest that even impairments in executive function and verbal fluency may be partly improved by transitioning chronically hospitalized patients to community-based living. Furthermore, as the participants in the present study continuously received well-planned comprehensive interventions based on the OTP (Mizuno et al., 2005; Ryu et al., 2006), it is reasonable to think that appropriate community services, in addition to living in a community, might have also contributed to the improvements in cognition seen in the subjects. Compared with their previous passive lifestyles,

Table 1
Changes in cognitive function over 5 years after transitioning to community-based living.

	Baseline		1 year		2 years		3 years		4 years		5 years		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F_{(5,275)}$	P
MMSE	26.0	3.0	26.0	3.0	26.3	3.4	26.9	2.8	27.1	2.5	26.3	3.9	2.824	0.032
LCT	105.8	12.6	109.8	8.8	110.8	3.5	110.3	4.4	110.9	3.9	109.7	8.4	6.775	0.002
DS														
Forward	5.2	1.9	4.9	1.9	4.9	1.9	4.9	1.8	4.8	1.8	4.9	2.1	1.590	0.163
Backward	4.1	1.5	4.3	1.4	4.3	1.6	4.1	1.5	4.0	1.6	4.1	1.5	0.981	0.430
ROCFT														
Immediate recall	32.8	3.3	32.8	3.3	33.7	2.9	33.3	3.3	33.7	2.4	33.7	2.6	2.530	0.040
Delayed recall	9.8	6.8	13.7	7.6	14.7	8.7	15.9	9.1	15.3	9.4	16.1	9.5	16.728	<0.001
WFT														
Letter fluency	15.8	8.1	17.9	8.6	18.7	9.5	20.5	11.2	19.5	10.2	18.7	10.3	7.138	<0.001
Category fluency	28.8	8.8	30.3	8.4	31.4	10.0	31.4	9.4	29.2	9.3	30.7	10.8	2.560	0.042
TMTA	213.8	86.5	190.6	74.4	173.0	66.2	189.0	79.8	192.7	99.2	188.1	74.7	3.109	0.020

Note: ANOVA, Analysis of Variance; MMSE, Mini-Mental State Examination; LCT, Letter Cancellation Test; DS, Digit Span; ROCFT, Rey–Osterrieth Complex Figure Test; WFT, Word Fluency Test; TMTA, Trail Making Test Part A.

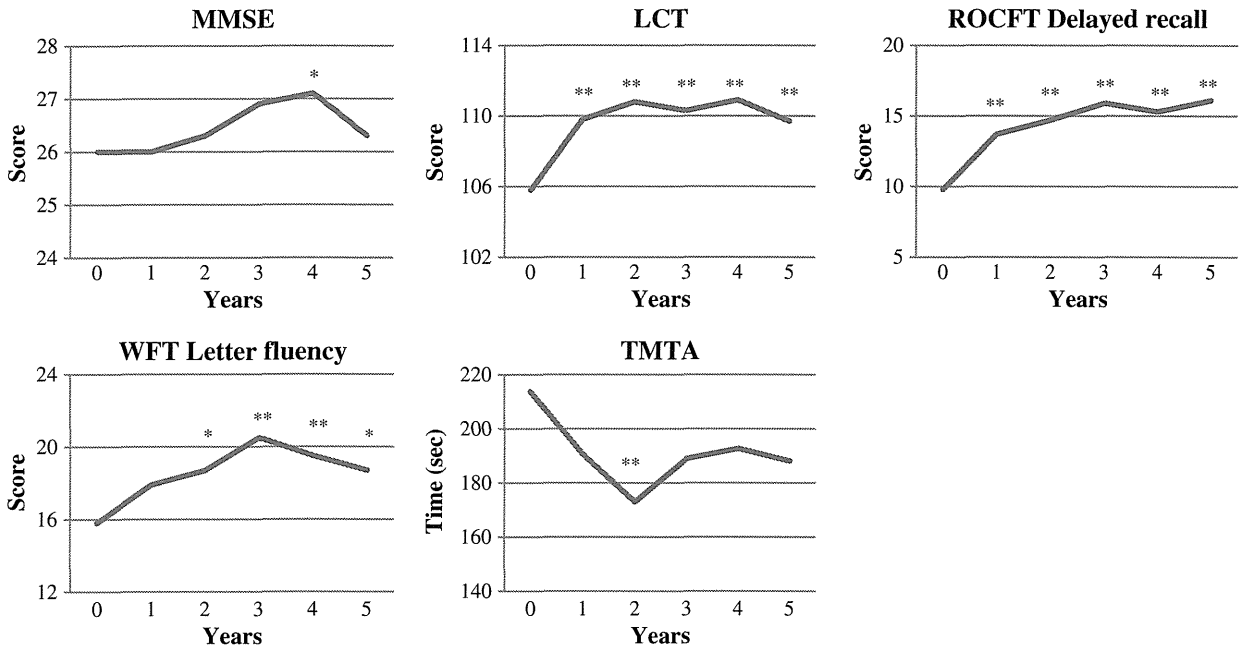

Fig. 1. Changes in cognitive functioning scores over 5 years after transitioning to community-based living. Note: MMSE, Mini-Mental State Examination; LCT, Letter Cancellation Test; ROCFT, Rey–Osterrieth Complex Figure Test; WFT, Word Fluency Test; TMTA, Trail Making Test Part A. *: $P < 0.05$. **: $P < 0.01$.

in which the hospital staff made decisions regarding their daily life, the transitioned patients experienced a dramatic change to an active lifestyle, in which they were expected to solve their own problems and to make decisions by themselves.

Global cognition and processing speed improved for a few years and then began to decline thereafter, although the patients' symptoms and global functioning improved consistently. This change might represent a genuine decline, and aging might have also influenced this decline, since the mean age of the subjects was almost 60 years at the end of the follow-up period. Some longitudinal studies suggest that patients with late-life schizophrenia start to decline cognitively at around the age of 65 years (Rajji and Mulsant, 2008), although this decline appears to be inconsistent with either normal aging or typical degenerative diseases (Davidson and Haroutunian, 1995).

4.2. Course of psychiatric symptoms and social functioning

Psychiatric symptoms and global functioning almost consistently improved over the 5-year follow-up period. A former report of our project revealed that psychiatric symptoms and social functioning improved during a 2-year follow-up period (Ryu et al., 2006). These findings are consistent with a previous study (Furlan et al., 2009), although the findings of published research examining the long-term course of symptoms and functioning after deinstitutionalization have varied. A review examining the long-term outcome of schizophrenia concluded that psychopathological symptoms generally remain relatively stable over the course of the illness (Lang et al., 2013). A large-scale prospective study on deinstitutionalization in London, the Team for the Assessment of Psychiatric Services (TAPS), described that social functioning improved but that psychiatric symptoms did not change (Trieman et al., 1996; Leff and Trieman, 2000). Mancevski et al. (2007) reported that the lifetime course of chronically hospitalized patients with schizophrenia is characterized by a decrease in positive symptoms and an increase in negative symptoms. Dwelling in the community while receiving adequate care may lead to an amelioration of symptoms and social functioning.

4.3. Predictor of functional outcome in 5 years

Performance on the category fluency test at baseline was extracted as a predictor of social functioning at 5 years, as measured using the SFS and the GAF among cognitive and demographic variables. However, it was no longer a significant predictor of functional outcomes when psychopathological variables were included as independent variables. The category fluency score was significantly correlated with the PANSS scores. These results suggest that cognitive function partly contributes to the longitudinal prediction of functional outcome in chronic patients with schizophrenia who are transitioning to the community. However, not all aspects of cognitive impairments appear to have an equivalent significance regarding the functional outcome. Verbal fluency has been reported to be correlated with social functioning in patients with schizophrenia (Green et al., 2000; Bowie et al., 2004). Depending on the task, category fluency demands a semantic search based on organization and logical associations within semantic

Table 2
Changes in psychiatric symptoms and social functioning over 5 years after transitioning to community-based living.

	Baseline		1 year		2 years		3 years		4 years		5 years		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F_{(5,275)}$	P
PANSS														
Positive symptoms	10.0	3.8	9.3	3.3	9.1	3.2	8.7	2.9	8.8	3.1	8.6	2.9	8.134	0.001
Negative symptoms	17.7	5.8	15.4	5.5	14.7	5.5	14.4	5.5	14.3	5.4	14.1	5.3	34.169	<0.001
General psychopathology	26.8	6.0	24.6	5.6	22.8	5.1	22.3	4.9	22.5	4.8	22.2	4.9	38.310	<0.001
SFS	112.2	22.6	114.0	19.2	112.2	21.0	112.5	18.6	111.1	21.5	109.2	20.8	1.155	0.332
GAF	57.5	13.5	62.7	10.0	64.1	10.9	67.2	11.8	64.9	11.8	65.4	12.2	17.841	<0.001

Note: ANOVA, Analysis of Variance; PANSS, Positive and Negative Syndrome Scale; SFS, Social Functioning Scale; GAF, Global Assessment of Functioning.

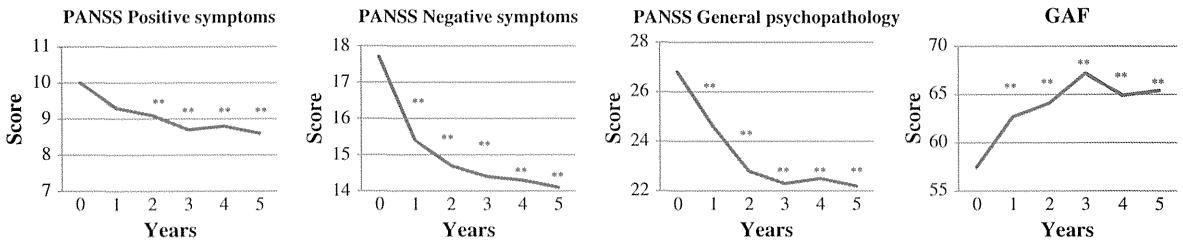

Fig. 2. Changes in psychiatric symptoms and social functioning over 5 years after transitioning to community-based living. Note: PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning. **: $P < 0.01$.

networks, whereas letter fluency demands a lexical search based on phonology; patients with schizophrenia exhibit differential impairments in category fluency, compared with letter fluency (Bokat and Goldberg, 2003). Such semantic fluency might contribute to functional outcomes that rely on producing solutions in social settings and navigating the complexities of social interactions to a greater degree than phonological fluency in patients with schizophrenia. We previously demonstrated that divergent thinking ability, as measured using fluency tests, contributed to community functioning in younger schizophrenic patients (Nemoto et al., 2007). Divergent thinking ability also appeared to be vital to elderly patients dwelling in the community, and cognitive remediation focusing on this ability may be useful, as it was in our previous study (Nemoto et al., 2009).

There are some limitations in the present study. It might have been preferable to set a control group for considering the practice effect of cognitive measures, although this did not seem practical. Furthermore, it is difficult to clarify which conditions are essential for optimizing cognitive and functional improvements following discharge because the participants dwelled in the community and several of them benefitted from various community services over a long period of 5 years. However, making sustained efforts to characterize cognitive impairments and their course might suggest clues to ameliorating impairments and the type of support that is most needed (Brier et al., 1991; Wykes, 1994).

Various efforts, including biological and pharmacological approaches as well as psychosocial ones, have been made towards improving cognitive function, even in chronic patients (Ehrenreich et al., 2007). The results of the present study suggest that care settings affect the course of cognitive function, and addressing these conditions may lead to a certain degree of cognitive improvement, even in schizophrenia patients who have been chronically institutionalized.

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Contributors

Masafumi Mizuno designed the study and wrote the protocol. Kei Sakuma was involved at the conceptualization level of the project. Yonosuke Ryu collected the data. Takahiro Nemoto and Hidehito Niimura analyzed the data. Takahiro Nemoto wrote the first draft of this manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Mismatch negativity and P3a/reorienting complex in subjects with schizophrenia or at-risk mental state

Yuko Higuchi[1], *Tomonori Seo*[1], *Tomohiro Miyanishi*[1], *Yasuhiro Kawasaki*[2], *Michio Suzuki*[1] *and Tomiki Sumiyoshi*[3]*

[1] Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Science, Toyama, Japan
[2] Department of Neuropsychiatry, Kanazawa Medical University, Ishikawa, Japan
[3] Department of Clinical Research Promotion, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

Edited by:
Ales Stuchlik, Academy of Sciences of the Czech Republic, Czech Republic

Reviewed by:
Julio Eduardo Arrnijo, Universidad de Santiago, Chile
Toshiaki Onitsuka, Kyushu University, Japan

***Correspondence:**
Tomiki Sumiyoshi, Department of Clinical Research Promotion, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8551, Japan
e-mail: sumiyot@ncnp.go.jp

Introduction: We measured duration mismatch negativity (dMMN), P3a, and reorienting negativity (RON) in subjects with at-risk mental state (ARMS), patients with first-episode or chronic schizophrenia, and healthy volunteers. The main interest was to determine if these event-related potentials provide a biomarker associated with progression to overt schizophrenia in ARMS subjects.

Methods: Nineteen ARMS subjects meeting the criteria of the Comprehensive Assessment of ARMS, 38 patients with schizophrenia (19 first-episode and 19 chronic), and 19 healthy controls participated in the study. dMMN, P3a, and RON were measured with an auditory odd-ball paradigm at baseline.

Results: During the follow-up period (2.2 years), 4 out of the 19 ARMS subjects transitioned to schizophrenia (Converters) while 15 did not (non-Converters). dMMN amplitudes of Converters were significantly smaller than those of non-Converters at frontal and central electrodes before onset of illness. dMMN amplitudes of non-Converters did not differ from those of healthy controls, while Converters showed significantly smaller dMMN amplitudes compared to control subjects. RON amplitudes were also reduced at frontal and central electrodes in subjects with schizophrenia, but not ARMS. Converter subjects tended to show smaller RON amplitudes compared to non-Converters.

Conclusions: Our data confirm that diminished dMMN amplitudes provide a biomarker, which is present before and after the development of psychosis. In this respect, RON amplitudes may also be useful, as suggested for the first time based on longitudinal observations.

Keywords: mismatch negativity, reorienting negativity, event-related potentials, prodromal, schizophrenia

INTRODUCTION

Schizophrenia is a disorder characterized by positive symptoms (hallucination, delusion, thought disturbance, etc.), negative symptoms (blunted affect, lack of volition, social withdrawal, etc.), and a range of disturbances of cognitive functions (Heinrichs and Zakzanis, 1998; Sumiyoshi et al., 2003; Harvey et al., 2004). In particular, cognitive impairment of schizophrenia is considered to largely determine the outcome of patients, including quality of life and social function (Green, 1996).

Prolonged duration of untreated psychosis (DUP) has been associated with poor long-term outcome, including work function, communication skills, and longer hospitalization (Loebel et al., 1992; Edwards et al., 1999; Malla et al., 2004; Melle et al., 2008; Yamazawa et al., 2008; Chang et al., 2011; Galderisi et al., 2012). On the other hand, shorter DUP has been related with a greater response to antipsychotic drugs in terms of symptoms and quality of life (Perkins et al., 2005). For these reasons, early detection, intervention, and treatment of schizophrenia are needed. In this context, it was reasonable that recent efforts have been directed to subjects with "at-risk mental state (ARMS)" or "ultra-high-risk patients" (McGorry et al., 2009).

The criteria for ARMS require that a young person aged between 14 and 30 years being referred for mental health difficulties met criteria for one or more of the following groups: (i) attenuated psychotic symptoms group (APS): have experienced sub-threshold, attenuated positive psychotic symptoms during the past year; (ii) brief limited intermittent psychotic symptoms group (BLIPS): have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated; or (iii) trait and state risk factor group: have a first-degree relative with a psychotic disorder or the identified client has a schizotypal personality disorder, and they have experienced a significant decrease in functioning during the previous year (Yung et al., 1996; Broome et al., 2005).

To promote early diagnosis, objective markers, particularly those based on brain morphology, neurophysiology, and neuropsychology, have been reported to provide useful information (Nakamura et al., 2004; Kawasaki et al., 2007b; Higuchi et al., 2008, 2013b; Takahashi et al., 2011; Takayanagi et al., 2011; Lin et al., 2012). Accordingly, event-related potentials (ERPs) have been suggested to provide a biomarker for cognitive impairment of schizophrenia.

P300 (P3a and P3b) and mismatch negativity (MMN) have been widely used for this purpose. Specifically, patients with schizophrenia have been reported to show smaller P300 amplitudes compared with normal control subjects (Roth et al., 1980; Kawasaki et al., 1997; Bruder et al., 1998). Also, P300 amplitudes have been shown to be reduced in subjects with ARMS (Ozgurdal et al., 2008). On the other hand, P300 is affected by various factors, including medication (Umbricht et al., 1998; Higuchi et al., 2008, 2013a; Sumiyoshi et al., 2009), suggesting the utility as a state marker of psychotic disorders.

Mismatch negativity is another component of ERPs generated in response to occasional variations (e.g., duration, frequency, intensity) of acoustic stimuli, which occurs about 100–200 ms after the onset of deviant stimulation, with peak amplitudes at fronto-central leads (Naatanen et al., 2007, 2012). MMN amplitudes have been suggested to reflect pre-attentive cognitive operations, and decreased in patients with schizophrenia, as indicated by a recent meta-analysis reporting a large effect size (Umbricht and Krljes, 2005). Unlike the case with P300, MMN amplitudes are generally not affected by psychotropic drugs, for example, benzodiazepines (Kasai et al., 2002) and dopamine antagonists (Leung et al., 2007). For these reasons, MMN is considered to provide a trait marker for schizophrenia.

Duration mismatch negativity (dMMN) amplitudes have been shown to be reduced already in the prodromal stage of the illness (Bodatsch et al., 2011; Jahshan et al., 2012; Shaikh et al., 2012; Higuchi et al., 2013b). Furthermore, smaller dMMN amplitudes have been reported in subjects with ARMS who later converted to overt psychosis, compared to those who did not (Shaikh et al., 2012; Higuchi et al., 2013b). Thus, reduced dMMN amplitudes are regarded to predict conversion to schizophrenia in at-risk subjects (Sumiyoshi et al., 2013).

P3a is a positive waveform that appears following MMN, i.e., between 250 and 300 ms after the presentation of stimuli. Its amplitudes are largest at fronto-central electrodes. The P3a component is assumed to reflect a pre-attentive index of deviance detection, and represent the involuntary capture of attention (Friedman et al., 2001).

A negative activity reflecting attentional "re"-orienting follows P3a. This component is referred to as reorienting negativity (RON) (Schroger and Wolff, 1998), which peaks at latencies between 400 and 600 ms, and is centered on fronto-central electrodes (Schroger and Wolff, 1998; Otten et al., 2000; Schroger et al., 2000). The MMN/P3a/RON complex has been shown to provide a neurophysiological index of the cascade of three main processes involved in involuntary attention controls (i.e., automatic change detection, orienting of attention, and reorienting of attention), following deviant stimuli (Berti et al., 2004; Horvath et al., 2008).

Investigations into this series of ERP components should provide further insights into cognitive disturbances in schizophrenia spectrum disorders, which have not been satisfactorily addressed. Specifically, there is little information about the RON in schizophrenia spectrum disorders. Jahshan et al. (2012) measured the amplitudes of MMN, P3a, and RON complex, and found reductions of these parameters in schizophrenia patients. Also, amplitudes of MMN and P3a, but not RON were diminished in individuals at-risk for psychosis. In spite of the above cross-sectional study, further work is needed to test the utility of the ERP complex for predicting progression to schizophrenia in vulnerable individuals.

In this study, we measured dMMN, P3a, and RON amplitudes in subjects with ARMS, first-episode schizophrenia (FES), or chronic phase of the illness. These data were compared with those of normal control subjects. We also attempted to determine if these ERP parameters would predict later progression to schizophrenia in ARMS subjects by means of longitudinal observations. Specifically, preliminary data are provided on the evaluation of RON in relation to transition to overt schizophrenia in vulnerable subjects.

MATERIALS AND METHODS

PARTICIPANTS

Diagnosis was made based on the Structured Clinical Interview for DSM-IV (SCID) for schizophrenia and the Comprehensive Assessment of At-Risk Mental State (CAARMS) for ARMS (Yung et al., 2005), by experienced psychiatrists. Most of these subjects were referred from Psychiatric Health and Welfare Center of Toyama (PHWCT), as previously described (Higuchi et al., 2013b). Nineteen ARMS subjects followed at the University of Toyama Hospital participated in this study [male/female = 9/10; mean (SD) age = 19.4 (3.6) years]. Thirty-eight schizophrenia patients also participated in this study. Patients with duration of illness <2 years were defined as FES [$n = 19$; male/female = 9/10; mean (SD) age = 22.8 (5.2) years], while those with duration of illness 2 years or longer were defined as chronic schizophrenia (CS) [$n = 19$; male/female = 9/10; mean (SD) age = 22.9 (3.6) years] (Higuchi et al., 2013b). The patients who allocated "first episode" are defined "single psychotic episode" and "duration of illness is <2 years." CS patients are defined "duration of illness is more than 2 years." Even if patients experienced only one psychotic episode, they allocated to CS group. We recruited normal control subjects from the community by advertisements. They are healthy volunteers [$n = 19$; male/female = 9/10; mean (SD) age = 19.4 (2.5) years] without any personal history of psychiatric illnesses, including schizophrenia or other psychotic disorders. All participants were right-handed. A psychiatric and treatment history was obtained from the subjects, families, and medical records. Subjects with a current history of substance abuse or dependence, seizure, or head injury were excluded from the study. Eligible patients had a complete physical examination and standard laboratory testing was normal. As clinical assessments, the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1990) were administered by an experienced psychiatrist. Demographic data at baseline evaluation are shown in **Table 1A**.

At-risk mental state subjects were followed-up at the hospital. Four out of the 19 ARMS subjects transitioned to schizophrenia during the observation period. When DSM-IV criteria were met, e.g., auditory hallucinations persisted or any delusion (for example, disturbance of the self) clearly observed, the subject was regarded to have converted to schizophrenia (Converters; Conv). Subjects who did not develop psychosis were defined as non-converters (Non-C). The average observation period for Non-C subjects was 2.2 ± 1.5 years.

Table 1 | (A) Demographic and clinical data; (B) ERP data.

(A)	Healthy controls ($n=19$)	ARMS ($n=19$)	First-episode schizophrenia ($n=19$)	Chronic schizophrenia ($n=19$)	Group comparison
Male/female	9/10	9/10	9/10	9/10	n.s.
Age (years)	19.4 (2.5)	19.4 (3.6)	22.8 (5.2)	22.9 (3.6)	$F(3,74)=4.94$, $p=0.004$
Age of onset (years)	–	–	22.2 (5.2)	17.9 (3.9)	$p=0.007$
Duration of illness (years)	–	–	0.7 (0.6)	5.0 (2.3)	–
Drug dose[a]	–	0.1 (0.4)	1.7 (2.0)	3.7 (4.2)	$F(2,56)=8.54$, $p=0.001$
SAPS	–	17.3 (7.4)	27.0 (16.9)	19.2 (18.0)	$F(2,56)=2.29$, $p=0.11$
SANS	–	60.8 (24.3)	60.6 (27.2)	53.3 (22.9)	$F(2,56)=0.52$, $p=0.59$

(B)	Healthy controls ($n=19$)	ARMS ($n=19$)	First-episode schizophrenia ($n=19$)	Chronic schizophrenia ($n=19$)	Analyze of variance (df = 3,75), group effect	
					F	*p*
dMMN amplitude (μV)						
F3	−6.9 (1.7)	−6.2 (2.0)	−5.0 (1.8)	−4.6 (1.0)	7.505	<0.001**
F4	−7.5 (1.4)	−6.5 (2.2)	−5.2 (2.1)	−4.6 (2.0)	7.767	<0.001**
Fz	−7.4 (1.4)	−6.5 (2.0)	−5.4 (1.9)	−4.8 (1.5)	8.322	<0.001**
Cz	−6.0 (1.4)	−5.6 (2.1)	−4.8 (1.9)	−3.7 (0.9)	6.831	<0.001**
Pz	−4.2 (1.4)	−4.5 (4.0)	−3.3 (1.4)	−2.2 (0.9)	6.240	0.001**
dMMN latency (ms)						
F3	167.3 (15.1)	172.1 (17.5)	173.0 (23.0)	177.8 (30.7)	0.702	0.55
F4	169.1 (15.4)	175.8 (18.3)	172.5 (19.7)	176.6 (24.0)	0.404	0.75
Fz	172.2 (15.6)	177.3 (12.6)	173.0 (19.1)	176.8 (25.6)	0.364	0.77
Cz	168.4 (14.8)	182.3 (18.7)	174.6 (16.7)	177.6 (26.2)	1.675	0.18
Pz	173.0 (15.8)	188.6 (24.4)	178.3 (17.4)	174.8 (30.7)	1.753	0.16
P3a amplitude (μV)						
F3	1.6 (1.8)	1.1 (1.4)	1.3 (2.2)	1.5 (1.3)	0.277	0.84
F4	1.4 (2.3)	1.2 (1.8)	1.6 (2.1)	1.4 (1.4)	0.110	0.95
Fz	2.0 (2.3)	1.7 (1.5)	1.7 (2.2)	1.7 (1.1)	0.179	0.91
Cz	2.4 (2.4)	2.1 (1.6)	2.5 (2.1)	2.1 (1.4)	0.209	0.89
Pz	2.0 (2.2)	1.8 (1.4)	2.3 (1.8)	1.8 (1.3)	0.408	0.74
P3a latency (ms)						
F3	255.6 (23.5)	265.2 (25.0)	264.2 (28.3)	262.8 (23.0)	0.395	0.75
F4	256.9 (20.2)	269.7 (28.0)	262.9 (31.1)	255.2 (30.8)	0.755	0.52
Fz	254.6 (21.5)	268.7 (28.8)	261.8 (30.9)	262.3 (22.3)	0.314	0.81
Cz	255.1 (21.7)	266.0 (25.9)	254.8 (28.7)	262.2 (22.9)	0.509	0.67
Pz	255.7 (19.8)	272.2 (27.2)	254.7 (27.6)	261.4 (19.7)	0.359	0.78
RON amplitude (μV)						
F3	−4.4 (1.7)	−4.1 (1.7)	−3.5 (1.3)	−3.3 (1.3)	2.320	0.08
F4	−5.2 (1.8)	−4.2 (1.5)	−3.6 (1.7)	−3.4 (1.6)	4.191	0.009**
Fz	−5.1 (1.6)	−4.2 (1.8)	−3.9 (1.4)	−3.4 (1.7)	3.143	0.03*
Cz	−4.3 (1.9)	−3.8 (2.1)	−3.6 (1.6)	−3.2 (1.6)	1.143	0.33
Pz	−3.1 (1.8)	−2.7 (1.7)	−2.5 (1.5)	−2.6 (1.6)	0.391	0.76
RON latency (ms)						
F3	396.3 (51.8)	380.7 (49.4)	395.0 (42.7)	389.0 (52.6)	0.395	0.75
F4	392.7 (53.9)	404.0 (54.1)	409.1 (53.1)	385.4 (53.8)	0.755	0.52
Fz	396.2 (50.2)	397.2 (46.8)	409.3 (40.9)	397.7 (53.3)	0.314	0.81
Cz	401.2 (39.0)	398.3 (44.4)	412.5 (40.9)	397.0 (47.4)	0.509	0.67
Pz	409.5 (48.2)	401.7 (45.7)	411.7 (40.7)	397.4 (58.2)	0.359	0.78

Values represent mean (SD).

[a]Risperidone equivalent (mg/day), ARMS, at-risk mental state; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

Values represent mean (SD). ARMS, at-risk mental state.

**p < 0.05, **p < 0.01.*