Intervention

For the CAP group, we will provide specialized early intervention teams by well-trained case managers and psychiatrists about their symptoms and daily activities for 18 months after enrollment. Case managers will promote participant recovery and social participation in cooperation with the early intervention team by using combination of cognitive behavioral therapeutic (CBT) approaches, psychoeducational approaches, family interventions, discharge support, and pharmacological therapy in accordance with the guidelines for FEP. The details of comprehensive community-based care are described later in the text. After 18 months, the participants will receive only standard care at each site. For the SC group, we will provide only standard care at each site throughout the entire study.

CBT approach

Several researches have suggested that CBT adapted to patients with early psychosis has effectiveness regarding their persistent positive symptoms, anxiety, and/or depression[15]. In this trial, we will not adopt structured CBT but needs-based CBT approaches in comprehensive community-based care. Case managers will receive basic CBT training and use the skills and techniques of CBT in comprehensive community-based care. The range and intensity of CBT will vary according to participant need as assessed by the early intervention team. Through CBT sessions, case managers will provide monitoring and coping skills for patients regarding their symptoms as well as functional skills for their daily lives.

Psychoeducational approach

Young people and their families rarely learn about symptoms, outcomes, and methods of coping with psychosis until they have mental illnesses; in other cases, they received incorrect information in addition to being subjected to discrimination and stigma. Therefore, they have significant stress and confusion because of the lack of information about psychosis. Several studies have suggested that psychoeducation is effective for relapse prevention, reducing hospital admission, and adherence of medication[16-18]. In this trial, the psychoeducational program for people with FEP will consist of sessions that provide not only information about etiology, symptoms, treatments, and outcome of psychosis, but also positive and helpful information toward functional recovery. In addition, we will provide psychoeducational programs for their families as described in the following section.

Family intervention

Family interventions will consist of 2 main domains of psychoeducation and family support for the family members of patients with mental illnesses. As described above, family members usually have little correct knowledge but a plethora of incorrect information and a great deal of stigma. Therefore, family members are also confused about methods of assisting patients who have recently exhibited psychotic symptoms. Several studies have suggested that family intervention for early psychosis is effective for relapse prevention, reducing hospital admission, and adherence of medication[19-21]. Family interventions for early psychosis will consist of psychoeducational programs and psychological therapy or counseling for families to relieve their burdens regarding the care of people with psychosis. Psychoeducational programs for families will consist of lectures about psychosis and peer group sessions. Psychological therapy and counseling for families will be provided through individual sessions.

Discharge support

More than 210,000 patients with schizophrenia stay in hospital for more than 1 year in Japan, mainly because of a lack of community mental health services[10]. This is particularly true for patients with psychosis for whom their family members are unable to obtain information and support from psychiatric community services. In this trial, case managers will encourage patients to live in their communities by introducing additional psychiatric community services, if needed.

Pharmacological therapy in accordance with the guidelines for FEP

Several pharmacological guidelines for schizophrenia and mood disorder are available worldwide. However, some psychiatrists in Japan have developed experimence-oriented strategies that result in polypharmacy for patients with schizophrenia[22]. Polypharmacy can exacerbate the negative symptoms and cognitive impairments of patients in addition to promoting dropped-out from treatment[22]. One reason why psychiatrists tend to prescribe more tablets may be that patients' treatment strategy and prescription are mainly decided by their psychiatrists who know little information except from the consultation with patients and their family members. In this trial, we will conduct regular meetings with early intervention teams and propose treatment and prescription strategies to psychiatrists according to the guidelines to eliminate unnecessary prescriptions.

Strategy for replacement from EIS

Recent studies about EIS for patients with FEP had negative results regarding the effectiveness of EIS discontinued in a longer term[23,24]. One reason may be that it is difficult to prepare patients to finish EIS and switch to normal services. On the basis of this result, we will emphasize "graduating from the EIS" and provide the policy of EI services to switch over to usual community services in order to easily maintain the effectives of EIS. Thus, we will also investigate whether this strategy for switch over will prolong the effectiveness of EIS.

Supervision for case management

To standardize the intensity and quality of EIS, we will conduct training courses at least twice a year with required participation by case managers at each site, at which they will have to discuss their practices and cases. Supervision in meetings will be provided, and professionals and supervisors of other services will discuss and provide advice about their practices and cases.

Outcomes and measurement items

We will adopt the function domain of the global assessment of functioning (GAF-F) [25] scores at the first end point as the primary outcome measure. Secondary outcomes will be GAF-F at the second and last end points, symptom domain of global assessment of functioning (GAF-S), PANSS,[12] the World Health Organization quality of life 26-item version (WHO-QOL26),[26,27] brief evaluation of medication influences and beliefs (BEMIB),[28] care satisfaction of participants and their families, educational and vocational recovery rates, remission rate, re-admission rate, lost to follow-up rate, self-harm and suicide attempt rate, suicide rate, engagement behavior, and direct and indirect costs at each end point. All measurement items will also be assessed at baseline. We will record the presence of comorbid mental and physical disorders and relevant sociodemographic and clinical information about the participants and their families at baseline and at each end point. The details of the assessments are discussed in the following sections.

GAF, GAF-F, and GAF-S

GAF records the current objective symptomatic and functional conditions of participants on one analogous scale ranging from 0 (poor) to 100 (good)[25]. GAF-F rates the social and occupational functions of patients, and GAF-S rates their symptoms. GAF is adopted as the worse score of GAF-F and GAF-S. We will also use the modified GAF scale [29] to measure GAF, GAF-F, and GAF-S.

PANSS

PANSS records the current objective symptoms of patients on 30 items[12]. PANSS consists of 3 domains: positive symptoms, negative symptoms, and general psychopathology. Each item is rated from 1 (absent) to 7 (extreme), and the total score ranges from 30 to 210.

WHO-QOL26

WHO-QOL26 [26,27] measures the current subjective satisfaction of participants regarding their quality of life on 26 items. WHO-QOL26 consists of 4 domains: physical health, psychological health, social relationships, and environment. Each item is rated from 1 (poor) to 5 (good) and presented as an average score.

BEMIB

BEMIB measures the current drug adherence of participants to their medications on 8 items[28]. Each item is rated from 1 (completely disagree) to 5 (completely agree), and the total score ranges from 8 to 40.

Care satisfaction

Care satisfaction will be measured by one simple item rated from 1 (very satisfied) to 4 (very dissatisfied). Participants and their families will provide subjective care satisfaction ratings after enrollment.

Recovery rate

Recovery will be measured by using the definition sheet adopted for EIS in England[30]. The item in the sheet termed "TRAINING AND OCCUPATION," which is rated from 0 (employment) to 4 (Not in Education, Employment or Training; NEET), will be assessed. For the initial assessment, this rating will be taken from the best occupational status achieved within the last 6 months for each end point taken from the point of last assessment.

Remission rate

We defined remission using a proposal from the Remission in Schizophrenia Working Group [31] that defined symptomatic remission of illness using 8 corresponding PANSS subscores (P1, P2, P3, N1, N4, N6, G5, and G9) of mild or less simultaneously on all items and for which remission regarding these scores was maintained for at least 6 months.

Re-admission rate

We will record all voluntary and involuntary admissions of participants at registration and during the follow-up period.

Lost to follow-up rate

Lost to follow-up will be defined at each end point as the refusal of further treatment despite the need and several attempts of reengagement (phone calls to patients and families in both groups and home visits to participants in the CAP group)[32]. We will consider the last successful contact the date of lost to follow-up.

Self-harm, suicide attempt, and suicide rate

Self-harm and suicide attempt will be measured using the items in the definition sheet "SELF-HARM and SUICIDE" on a scale of 0 (None) to 4 (Severe problems) [30]. We will assess the inquiry sheets for all of the suicide and severe self-harm actions at all sites.

Engagement behavior

Engagement, family engagement, and social relationships will be measured using the items in the definition sheet "ENGAGEMENT, FAMILY/CARER ENGAGEMENT, and RELATIONSHIPS" on a scale of 0 (Severe problems) to 4 (Very good) [30].

Service costs and cost-effectiveness

Service costs will be calculated using the Client Service Receipt Inventory (CSRI),[9,33], which can estimate service costs and cost-effectiveness, particularly in psychiatric contexts. On the basis of the CSRI, we will conduct interviews of daily living (e.g., service use, school,

employment, and family conditions) at registration, at each end point, and if possible, at intermediate points between end points. Service costs will be calculated by the service costs and appropriate local unit costs. Cost-effectiveness will be calculated by the combination of the outcomes related to the service costs and participant subjective quality of life assessments using WHO-QOL26. Unavailable cost data will be estimated using other resources and models.

Data reliability

Some methodological problems regarding interrater reliability will exist. To control the quality of data assessment, we will conduct lectures for PANSS and GAF, including GAF-F and GAF-S, more than once a year using video movies to ensure accurate scoring. We will also calculate interrater reliability for PANSS and GAF scores provided by the raters in the lecture, and we will provide feedback for these results to maintain a high quality of assessment.

Sample size

The planned number of participants is 150, as determined by previous RCT results, the clustering effects of each site, and the possibility of exhaustion of our resources. An RCT of EIS for patients with FEP in Holland indicated that EIS improved participant GAF-F scores in 24 months[5]. Another RCT of CBT in England revealed that CBT improved patient readmission rates and GAF scores in 18 months[6,7]. The effect sizes calculated from their results were 0.26, 0.46, and 0.58, respectively. The estimated sample sizes using G*Power 3[34] (alpha error = 0.05, beta error = 0.2) were 370, 150, and 96, respectively.

We will adopt 1 interim analysis and consider stopping the trial if the participants in the CAP group have unexpected effective outcomes compared with those in the SC group. We will conduct the interim analysis when half of the participants finish the trials until the first end point. Stopping rules will be planned on the basis of the O'Brien-Fleming method [35] for the GAF-F score, re-admission rate, lost to follow-up rate, self-harm and suicide attempt rate, and suicide rate at the first end point. We will consider stopping the trial on the basis of the stopping rule, baseline data, missing data, and site. Because of ethical issues, we will provide EIS to all participants until 18 months after allocation if the trial is halted.

Randomization

Enrollment and random allocation will be performed by central registration at the University Hospital Clinical Trial Alliance Clinical Research Supporting System (UHCT ACReSS) at the University of Tokyo. The managers of each site will enroll participants after examining their eligibility and informed consent. The type of allocation will be stratified and block randomization. We will adopt stratification as sites and inpatients/outpatients at enrollment. Owing to allocation concealment, the block size will be provided by UHCT ACReSS and will not be revealed to any researchers or staff until the end of the enrollment period. As this is a single-blinded trial, all assessments after enrollment will be conducted by independent raters with no knowledge of any treatment and care provided this trial.

Statistical method

All findings will be reported according to the revised CONSORT statement[36]. All analyses will be performed using SPSS 17.0 J (SPSS Inc., Chicago, IL, USA). All data will be analyzed under the intent-to-treat principle. The primary outcome will be analyzed using a simple Student's t test and analyzed regarding potential confounders (e.g., age, gender, sociodemographic factors, site, and clinical characteristics) using regression models. Secondary outcomes will be analyzed using relevant tests at each end point and for possible confounders as described for the primary outcome. Subgroup analysis will be conducted at sites and performed for any possible confounders to differentiate the effectiveness of each situation and explore cluster effects.

Discussion

This trial has some possible limitations regarding sample size and the duration of case management. Previous studies of EIS for patients with FEP have suggested that although 1.5-year EIS improved patient social functions and readmission rates, these effects did not persist (5 years)[23,24]. However, these results also depend on the treatment provided to the control group, and community mental health services are widely available in Holland and England[1]. In the present situation in Japan, little psychological education is provided in schools and the workplace, and few mental health services are available in the community setting; consequently, much prejudice, discrimination, and stigma exists regarding psychosis[10]. In addition, we will emphasize "graduating from the service" in that case managers will continue to provide services after EIS after a participant enrolls in the trial. Therefore, this trial will demonstrate the effectiveness of EIS in Japan and also explore and consider exit strategies for EIS. Finally, the results of this trial will be used to inform policy makers and practitioners about the benefits, required human resources, and cost-effectiveness of EIS. This trial will provide helpful results about the effectiveness and cost-effectiveness of EIS in Japan to improve the quality and quantity of community mental services.

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Authors' contributions
SK and AN equally contributed to design and management in this trial, and wrote most of the manuscript. SY made substantial contributions to conception and design of this trial and wrote the manuscript with regard to psychosocial care. KI, SM, TN, and HH made substantial contributions to conception and design of this trial. KK, IF, MH, and YO are the directors at each site and made substantial contributions to the revision of the design and management in this trial. All authors read and approved the final manuscript.

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Psychotic-like experiences are associated with violent behavior in adolescents

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ABSTRACT

Objective: The diagnosis of psychotic disorder is associated with a risk of violence. Psychotic-like experiences (PLEs) in the general population may share an etiological background with psychotic disorders. The present study has evaluated the association between PLEs and violent behavior in adolescents.
Methods: PLEs and violent behavior were assessed using a self-report questionnaire administered to 18,104 Japanese adolescents. Potential confounding factors were also evaluated.
Results: After controlling for the effects of age, gender, GHQ-12 total score, victimization, and substance use, the existence of PLEs was significantly associated with both interpersonal violence (odds ratio (OR) = 1.36, 95% confidence interval (CI): 1.23 to 1.51) and violence towards objects (OR = 1.46, 95%CI: 1.33 to 1.61). The greater the number of such psychotic experiences, the higher the risk of violence. Particular types of PLEs ('spied-upon' and 'voice hearing') are significantly associated with interpersonal violence, while all of the types of PLEs assessed in this study were significantly associated with violence towards objects.
Conclusion: PLEs may be a risk factor for violent behavior in adolescents. Violent acts by individuals with schizophrenia may not be a direct consequence of the disease itself, but may instead share an etiological background with such behavior in the general population.

1. Introduction

Recent studies suggest that positive psychotic symptoms exist on a continuum, with psychotic disorder at one end and non-clinical psychotic-like experiences (PLEs) at the other (Stip and Letourneau, 2009; van Os et al., 2000; Verdoux and van Os, 2002). Indeed, PLEs are a common phenomenon in the general population, including adolescents. For instance, in a large sample of more than 7000 men and women aged between 18 and 64 taken from the general population, van Os et al. (2000) revealed that 17.5% of the participants had reported at least one experience evoking the concept of psychosis. Furthermore, some studies have suggested that PLEs in childhood and adolescence may be risk factors for later psychiatric disorders and harmful behavior, including violence (Chapman et al., 1994; Nishida et al., 2010; Poulton et al., 2000; Mojtabai, 2006).

Violence is one of the most problematic behaviors in adolescence, and is also associated with the diagnosis of a

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psychotic disorder including schizophrenia (Junginger, 1996; Swanson et al., 2006; Walsh et al., 2002; Douglas et al., 2009). However, little is known about the potential mechanisms for the association between psychosis and violence (Foley et al., 2005, 2007). It is possible that violent behavior in individuals with schizophrenia can be explained by the continuum hypothesis (Stip and Letourneau, 2009; van Os et al., 2000; Verdoux and van Os, 2002), in which violence is also associated with non-clinical psychotic-like experiences. It may also be the case that such behavior in individuals diagnosed with psychotic disorders shares an etiological background with those in the general population. It is, therefore, valuable to examine if PLEs are associated with violent behavior in a non-clinical population. It is particularly important to confirm this potential association in adolescents, since this time of life is the peak period for violence (Reiss and Roth, 1993), and the onset of schizophrenia typically occurs after the late teens (Verdoux et al., 1998).

Although some research has revealed that PLEs were associated with violent behavior in the general population (Mojtabai, 2006), to our knowledge, few studies have reported an association between PLEs and violence among adolescents. Moreover, earlier research into the link between PLEs and violent behavior did not distinguish between interpersonal violence and violence towards objects, and nor did it examine if there is any difference between early and late adolescence.

The present study, therefore, aims to examine the contribution of PLEs to the occurrence of violent behavior in adolescents. The two hypotheses we would like to examine are:

1) Whether interpersonal violence and violence towards objects are directly associated with PLEs in adolescents.
2) Whether specific types of PLEs are associated with interpersonal violence and violence towards objects in adolescents.

2. Methods

2.1. Sample and survey procedures

In order to investigate the psychopathology in adolescence and examine its associated factors such as demographics, victimization and help seeking attitudes, we conducted a large community survey in Japan. This report focused on violence and its associated factors in adolescence. Between 2008 and 2009, we recruited students (aged between 12 and 18 years) from 45 public junior high schools (7th–9th grades) and 28 high schools (10th–12th grades) in Tsu City and Kochi Prefecture, Japan. We then conducted a cross-sectional survey of psychopathologies in this sample. The total populations of Tsu City and Kochi Prefecture are approximately 280,000 and 790,000 respectively. Attendance at junior high school is compulsory under the Japanese law, but attendance at high school is not.

After the study was approved by the ethics committees of the Tokyo Institute of Psychiatry, the Mie University School of Medicine and the Kochi Medical School, the principal investigators approached the schools' head teachers about participation in the research. These heads then consulted with teachers and parents.

The teachers at the participating schools were told about the guidelines for the distribution and collection of our questionnaires. They then gave these documents to the students, along with envelopes in which to place them after completion of the task. The teachers also explained: 1) that participation in the study was anonymous and voluntary, and 2) that strict confidentiality would be maintained. In addition, the students were asked to seal the completed questionnaire in the envelope they had been provided with. Each teacher also reported on the total number of present and absent students on the day the survey was administered (including those who had not been in attendance for more than a month). The research team later collected the sealed questionnaires from each school.

2.2. Measures

The questionnaires included items concerning the following: 1) psychopathological and behavioral problems, including PLEs, interpersonal violence and violence towards objects; 2) the Japanese version of the 12-item General Health Questionnaire (GHQ-12); and 3) other variables, including demographic characteristics.

2.2.1. Psychotic-like experiences

Psychotic-like experiences were assessed using five items adopted from the schizophrenia section of the Diagnostic Interview Schedule for Children (DISC-C) (Costello et al., 1985). These items have previously been used in a birth cohort study and are regarded as good predictors of schizophreniform disorder in adulthood (Poulton et al., 2000). The items were as follows: 1) "Some people believe in mind reading or being psychic. Have other people ever read your mind?"; 2) "Have you ever had messages sent just to you through the television or radio?"; 3) "Have you ever thought that people are following you or spying on you?"; 4) "Have you ever heard voices other people cannot hear?"; and 5) "Has something ever gotten inside your body or has your body changed in some strange way?". The participants were told that they should base their answers on whether they had ever experienced these symptoms at any point in their life. Possible responses included: 'no', 'yes, likely', and 'yes, definitely (only once or more than once)'. We defined 'yes, definitely' as the presence of a hallucinatory and delusional experience, and 'no' or 'yes, likely' as no experience. The number of experiences reported by an individual was designated as the 'total PLE score', with a range of 0–5. In addition, the number of delusional experiences reported by an individual was denominated as the 'delusional score of PLE', with a range of 0–4.

2.2.2. Interpersonal violence and violence towards objects

Questions about interpersonal violence and violence towards objects in the previous year were also included in the questionnaire. These two items were: "Have you physically abused someone in your family or your friends?" (for interpersonal violence within the past year) and "Have you been extremely frustrated and damaged something?" (for violence towards objects within the past year). There were two possible responses to these questions: 'yes' or 'no'. There is evidence that self-reports of violence correspond

reasonably well with administrative records (Crisanti et al., 2005). Suicide was not included in the violent behavior in the present study.

2.2.3. The GHQ-12

The GHQ-12 is one of the most widely used self-report screening tools for non-psychotic psychiatric symptoms, particularly those of anxiety and/or depression (Goldberg et al., 1976). The validity and reliability of the Japanese version of the test have been confirmed (Doi and Minowa, 2003; Fukunishi, 1990). The GHQ was originally applied to adult populations, but was then used and validated for younger groups (Arakida et al., 2003; Kaneita et al., 2007; Radovanovic and Eric, 1983; D'Arcy and Siddique, 1984). A 4-point scale, with binary scoring (0011), which is known as the GHQ method, was used for each of the questions. Responses of '1' were then added together to form the total score, with a range between 0 (best possible) and 12 (worst possible). Individuals with a total GHQ-12 score ≥4 were considered to have poor mental health (Arakida et al., 2003; Fuchino et al., 2003; Kaneita et al., 2007). The total GHQ score was demonstrated to be associated with both PLEs (Nishida et al., 2008) and violence (Blitstein et al., 2005), and could be a potential confounding factor influencing the link between PLEs and violence.

2.2.4. Other variables

Violent behavior among a young population might be influenced by other confounding factors, such as victimization and substance use, as indicated in previous studies (Campbell and Morrison, 2007; Lataster et al., 2006; Hovens et al., 1994; Swanson et al., 1990; Spidel et al., 2010). In our questionnaire, we asked the participants about their experiences of being bullied (within the past year), violence from adults at home (within the past month), alcohol use (within the past month), and the use of recreational drugs (lifetime). The items concerning victimization ('being bullied' and 'violence from adults in the home'), alcohol use, and the use of recreational drugs were answered with a 'yes' or a 'no'.

2.3. Statistical analysis

Associations between PLEs and violent behavior in the previous year were analyzed using a logistic regression analysis, adjusted for age, sex, GHQ-12 total score, victimization ('being bullied' and 'violence from adults in the home') and substance use (alcohol use and the use of recreational drugs). In addition, the effect of the total PLE score was also tested. Interpersonal violence and violence towards objects were the dependent variables.

Associations between each of the five PLEs and the two types of violent behavior were examined by comparing individuals who had experienced each type of PLE to those who had not. A logistic regression analysis was again used to control for possible confounding factors. Additionally, in order to evaluate the effects of a combination of delusional and hallucinatory experiences on violence, we conducted another logistic regression analysis, adjusted for the potential confounding factors. ORs for the delusional score of PLE, voice hearing, and the interaction term for both of these factors were calculated through the analysis.

All of the statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-tailed P-value<0.05 was considered to be statistically significant.

3. Results

3.1. Descriptive statistics

13 of 20 public junior high schools in Tsu City, and 32 of the 118 public junior high schools and 28 of the 36 public high schools in Kochi Prefecture, agreed to participate in the survey. Of all of the students in the relevant classes invited to take part (n=19,436), 18,638 were approached at school (798 were absent), of whom 18,250 agreed to contribute to the research. Of these 18,250 subjects, 18,104 (93.1% of all students in the relevant classes) gave analyzable responses. Of these 18,104 participants, 8992 were male (49.7%) and 9112 were female (50.3%). Their ages ranged from 12 to 18, with the mean age being 15.2 (SD=1.7). The mean and median of the total GHQ score were 3.53 (SD=3.15) and 3.00, respectively.

3.2. Prevalence of PLEs and violent behavior

The prevalence of the five PLEs was as follows: 'thoughts read' was observed in 343 individuals (1.9%), 'special messages' in 133 (0.7%), 'spied-upon' in 1157 (6.4%), 'voice hearing' in 1743 (9.6%), and 'somatic ideation' in 338 (1.9%). In addition, 2611 (14.4%) reported at least one type of PLE. In the previous 12 months, the two types of violent behavior with which we were concerned were reported by 4301 (23.8%) (interpersonal violence) and 6353 students (35.1%) (violence towards objects), respectively.

3.3. Associations between PLEs and violent behavior

The occurrence of at least one type of PLE was associated with an increased prevalence of both interpersonal violence and violence towards objects, even after controlling for age, sex, non-psychotic psychiatric symptoms (the GHQ-12 total score), victimization, and substance use (Table 1). There was no difference between high school (late adolescents, aged 15–18) and junior high school students (early adolescents, aged 12–15) in terms of trends in association between PLEs and violent behavior. Furthermore, the OR (adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ-12 total score) for a one point increase in the total PLE score was 1.15 (95%CI: 1.08 to 1.22; p<0.001) for interpersonal violence and 1.28 (95%CI: 1.20 to 1.36; p<0.001) for violence towards objects. This indicates that these behaviors were more prevalent in individuals who had experienced a greater number of PLEs. Table 2 sets out the associations between the potential confounding factors and violence. All the factors except for alcohol use were independently associated with both interpersonal violence and violence towards objects. The relationship between alcohol use and interpersonal violence was statistically significant, though the association of alcohol intake to violence towards objects was not.

Table 1
Associations between violent behaviors in the previous year and the lifetime occurrence of at least one type of PLE.

	Whole sample [a]				Junior high school				High school			
	Unadjusted OR (95%CI)	P	Adjusted OR [b] (95%CI)	P	Unadjusted OR (95%CI)	P	Adjusted OR [b] (95%CI)	P	Unadjusted OR (95%CI)	P	Adjusted OR [b] (95%CI)	P
Interpersonal violence	1.97 (1.81, 2.16)	<0.001	1.36 (1.23, 1.51)	<0.001	1.84 (1.63, 2.07)	<0.001	1.31 (1.14, 1.50)	<0.001	2.05 (1.78, 2.36)	<0.001	1.43 (1.22, 1.67)	<0.001
Violence towards objects	2.32 (2.13, 2.53)	<0.001	1.46 (1.33, 1.61)	<0.001	1.99 (1.80, 2.20)	<0.001	1.43 (1.25, 1.63)	<0.001	2.18 (1.93, 2.46)	<0.001	1.49 (1.30, 1.70)	<0.001
Interpersonal violence and/or violence towards objects	2.36 (2.16, 2.57)	<0.001	1.50 (1.36, 1.65)	<0.001	2.40	<0.001	1.46	<0.001	2.24	<0.001	1.53	<0.001

[a] In each section, the sample size ranged between 17,192 and 17,631 due to the missing data that have been excluded from the statistical analyses.
[b] Odds ratio adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score.

3.4. Associations between specific PLEs and violent behavior

The effect of each of the five PLEs was analyzed by a logistic regression analysis. After controlling for age, sex, non-psychotic psychiatric symptoms (the GHQ-12 total score), victimization, and substance use, 'being spied-upon' and 'voice hearing' were significantly associated with interpersonal violence, while 'thoughts read', 'special messages' and 'somatic ideation' were not. All of the assessed PLEs ('thoughts read', 'special messages', 'spied-upon', 'hearing voices', and 'somatic ideation') were significantly related to violence towards objects (Table 3).

3.5. Effects of a combination of delusional and hallucinatory experiences on violence

Table 4 portrays the ORs (adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score) for the delusional score of PLE, voice hearing, and the interaction term for both of these factors for violence. The ORs for the interaction term for the delusional score of PLE and voice hearing were 0.72 (95%CI: 0.60 to 0.86) for interpersonal violence and 0.77 (95%CI: 0.64 to 0.93) for violence towards objects.

4. Discussion

The present study has confirmed that PLEs are associated with the occurrence of interpersonal violence and violence towards objects in a large, locally-representative sample of adolescents (n = 18,104). A dose–response association was highlighted between the number of PLEs and the violent behavior; the greater the number of psychotic-like experiences, the higher the risk of the violence. No difference was found between high school (late adolescents, aged 15–18) and junior high school students (early adolescents, aged 12–15) in terms of trends in association between PLEs and violent behavior. With regard to the relationship between other important factors and violent behavior, this research replicated the previous one which demonstrated the significant associations of sex, age, poor mental health, victimization and substance use to violent behavior (Swanson et al., 1990;

Table 2
Associations between violent behaviors in the previous year and the potential confounding factors.

	Interpersonal violence		Violence towards objects		Interpersonal violence and/or violence towards objects	
	Adjusted OR [a] (95%CI)	P	Adjusted OR [a] (95%CI)	P	Adjusted OR [a] (95%CI)	P
Sex [b]	0.50 (0.46, 0.54)	<0.001	0.70 (0.65, 0.75)	<0.001	0.60 (0.56, 0.64)	<0.001
Age [c]	0.77 (0.75, 0.79)	<0.001	0.92 (0.90, 0.94)	<0.001	0.84 (0.83, 0.86)	<0.001
GHQ total score [d]	1.11 (1.10, 1.13)	<0.001	1.21 (1.19, 1.22)	<0.001	1.20 (1.19, 1.22)	<0.001
Being bullied	1.45 (1.27, 1.65)	<0.001	1.15 (1.01, 1.30)	<0.05	1.31 (1.15, 1.49)	<0.001
Violence from adults in the home	3.21 (2.69, 3.82)	<0.001	2.11 (1.77, 2.52)	<0.001	2.63 (2.16, 3.21)	<0.001
Alcohol use	1.70 (1.54, 1.89)	<0.001	1.96 (1.78, 2.15)	<0.001	1.99 (1.81, 2.19)	<0.001
Use of recreational drugs	1.26 (1.05, 1.52)	<0.05	1.15 (0.95, 1.39)	<0.14	1.20 (0.98, 1.47)	<0.08

In each section, the sample size ranged between 17,192 and 17,631 due to the missing data that have been excluded from the statistical analyses.
[a] Odds ratio calculated through the regression analyses conducted to obtain the adjusted ORs presented in Table 1.
[b] Male was used as referent.
[c] ORs were calculated for a one year increase in age.
[d] ORs were calculated for a one point increase in the GHQ total score.

Table 3
Associations between violent behaviors and specific PLE.

	Interpersonal violence		Violence towards objects	
	Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)	Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)
Thoughts read	1.56 (1.24, 1.96)	0.99 (0.76, 1.28)	2.37 (1.91, 2.94)	1.64 (1.29, 2.10)[b]
Special messages	2.45 (1.73, 3.46)	1.29 (0.85, 1.95)	3.24 (2.27, 4.63)	2.03 (1.33, 3.11)[c]
Spied-upon	2.03 (1.79, 2.30)	1.35 (1.17, 1.56)[b]	2.66 (2.36, 3.00)	1.56 (1.36, 1.78)[b]
Hearing voices	1.96 (1.76, 2.17)	1.26 (1.12, 1.42)[b]	2.24 (2.02, 2.47)	1.38 (1.23, 1.54)[b]
Somatic ideation	2.10 (1.68, 2.62)	1.06 (0.82, 1.38)	2.93 (2.34, 3.65)	1.46 (1.13, 1.88)[c]

In each section, the missing data have been excluded from the statistical analyses.
[a] Odds ratio adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score.
[b] $p<0.001$.
[c] $p<0.01$.

Blitstein et al., 2005; Spidel et al., 2010). The study also revealed that particular types of PLEs ('spied-upon' and 'voice hearing') are significantly associated with interpersonal violence, while others are not significantly related to this type of violent behavior. On the other hand, all of the types of PLEs assessed in this study were significantly associated with violence towards objects.

These results suggest that PLEs may contribute to violent behavior, and that such behavior in individuals with schizophrenia may be at least partially explained by the continuum hypothesis (Stip and Letourneau, 2009; van Os et al., 2000; Verdoux and van Os, 2002). This is when violent behavior is not directly caused by a psychotic disorder as a discrete entity, but is mediated by the psychotic symptoms which exist on a continuum from normal experiences. In other words, violence in individuals diagnosed with psychotic disorders may share an etiological background with such behavior in the general population. Accordingly, early detection and intervention targeted at PLEs may be needed to prevent the harmful behaviors by adolescents with these experiences.

Mojtabai (2006) suggested that PLEs are associated with interpersonal violence in a dose–responsive manner in the general population. Our results have confirmed that the same association exists in adolescents, even when possible confounding factors are controlled for by conducting a multivariate binary logistic regression analysis.

Table 4
Effects of a combination of delusional and hallucinatory experiences on violence.

	Adjusted OR[a] for interpersonal violence (95%CI)	Adjusted OR[a] for violence towards objects (95%CI)
Delusional score of PLE[b]	1.31 (1.15, 1.50)[c]	1.49 (1.31, 1.70)[c]
Voice hearing	1.34 (1.17, 1.54)[c]	1.33 (1.17, 1.51)[c]
Interaction term for delusional score of PLE and voice hearing	0.72 (0.60, 0.86)d	0.77 (0.64, 0.93)[d]

In each section, the missing data have been excluded from the statistical analyses.
[a] Odds ratio adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score.
[b] ORs were calculated for a one point increase in the delusional score of PLE.
[c] $p<0.001$.
[d] $p<0.01$.

Previous studies have reported that a particular sub-group of delusions, which provoke threat and control override characteristics, represents an important risk factor for violence in both the general population and a number of patient groups (Link et al., 1998; Cheung et al., 1997; Swanson et al., 2006). Our data suggests that when it comes to adolescents, this conclusion can only be applied to interpersonal violence, but not to violent behavior towards objects. Moreover, the present study also suggests that sub-clinical auditory hallucinations may be an important risk factor for the two types of violence in this population. Conceivably, the association between voice hearing and interpersonal violence is mediated by the threat and control override characteristics displayed in the contents of this type of experience. However, the same explanation cannot be applicable to the association between voice hearing and violence towards objects, because all of the other PLEs, including those without threat and control override characteristics, were proved to be significantly associated with this type of violent behavior.

This discrepancy between interpersonal violence and violence towards objects implies that threat and control override characteristics of delusions or hallucinations are not needed to induce violent behavior. This theory could be validated by the findings by Teixeira and Dalgalarrondo (2009) suggesting that delusional patients who are frightened or who have other negative affects related to delusional ideas appear to commit fewer violent acts. If this is the case, then some unknown factors such as accompanying anxiety might determine the significance of each type of PLEs in provoking violence. It may well be the unknown factors that may define the three major roles of psychosis in inducing violence: 1. in focusing (organizing) decision and behavior, giving individuals a clear motivation for violence, 2. in destabilizing (disorganizing) decisions and behavior, interfering with the ability of individuals to manage interpersonal conflicts, and 3. disinhibiting role in violence (Douglas et al., 2009).

Contrary to an indication in a previous study using a resident sample of high security hospital patients (Taylor et al., 1998), a combination of delusional and hallucinatory experiences did not seem more significantly associated with violent behavior than either alone in the community sample of adolescence. The difference in the characteristics of the samples might lead to this discrepancy.

There are several limitations with this research. Firstly, our survey was cross-sectional, meaning that there may be

some respondents for whom violence occurred before the onset of their PLEs. Accordingly, it is impossible to demonstrate an actual causal relationship between PLEs and violent behavior. In other words, the results in the present study could be interpreted as meaning that violent behavior could predict PLEs. Indeed, Gosden et al. (2005) demonstrated that violence predicts the diagnosis of schizophrenia. Nevertheless, in the questionnaire used in our survey, the participants were told that they should base their answers about PLEs on whether they had ever experienced these symptoms at any point in their life, while information about interpersonal violence and violence towards objects was based on experiences in the previous year. This design of questionnaire could increase the possibility that PLEs temporally precede the occurrence of violent behavior.

Secondly, the two types of violent behavior were only assessed by self-reporting on the part of the participants, and not by informant reports. Self-reported violence may lead to misclassification and an under or over-estimation of the prevalence of these behaviors. Nevertheless, there is evidence that self-reports of violence correspond reasonably well with administrative records (Crisanti et al., 2005), as described in Section 2.2.2. Though Stompe et al. (2004) suggested that the threat/control override factor of delusion was not associated with violence but with severity thereof, we could not re-examine these findings with our data, because we did not evaluate the seriousness of the violent behavior.

Thirdly, as this was a school-based survey, we were unable to obtain answers from absent students. Yet, violent behavior and/or PLEs may be more prevalent among those who are frequently absent from school, as well as those who have been off for a long time. Accordingly, an association between violence and PLEs in this study may well be under or over-estimated.

Fourthly, we did not include a number of relevant factors (i.e. conduct disorder, oppositional defiant disorder, antisocial personality disorder and socioeconomic status) in the potential confounding factors. Though these factors have been demonstrated to be important predictors of violence in psychotic people (Douglas et al., 2009; Coid et al., 2006; Goethals et al., 2008), no assessment was done with regard to these variables in our survey.

In addition, because of the very large sample size, even a small amount of difference could be shown statistically significant. Moreover, we cannot exclude the possibility that some portion of participants may be prodromal for or diagnosed with schizophrenia.

In conclusion, PLEs may predict both interpersonal violence and violence towards objects in adolescents. Of the five types of psychotic-like experiences considered, those of 'being spied-upon' and 'voice hearing' were particularly associated with interpersonal violence, while all of the assessed PLEs were significantly related to violence towards objects. Consequently, early detection and intervention for PLEs may be needed before they lead to harmful behavior. Additionally, violent acts by individuals with schizophrenia may not be a direct consequence of the disease itself, but may instead share an etiological background with such behavior in the general population. Further investigations could be conducted to give a clearer picture of the mechanism which links PLEs to violent behavior in adolescents.

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Contributors

Dr. Y. Kinoshita designed the study, undertook the statistical analysis, and interpreted the data. Drs. Nishida, Sasaki and Okazaki designed the study and wrote the protocol. Drs. Nishida and Shimodera collected the data. Drs. Y. Kinoshita and Furukawa wrote the first draft of the manuscript. Dr. K. Kinoshita managed the literature searches. Drs. K. Kinoshita, Watanabe, Akechi, Oshima and Inoue revised the first draft critically. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

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Localized gray matter volume reductions in the pars triangularis of the inferior frontal gyrus in individuals at clinical high-risk for psychosis and first episode for schizophrenia

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ABSTRACT

Recent studies have suggested an important role for Broca's region and its right hemisphere counterpart in the pathophysiology of schizophrenia, owing to its roles in language and interpersonal information processing. Broca's region consists of the pars opercularis (PO) and the pars triangularis (PT). Neuroimaging studies have suggested that they have differential functional roles in healthy individuals and contribute differentially to the pathogenesis of schizophrenic symptoms. However, volume changes in these regions in subjects with ultra-high risk for psychosis (UHR) or first-episode schizophrenia (FES) have not been clarified. In the present 3 Tesla magnetic resonance imaging study, we separately measured the gray matter volumes of the PO and PT using a reliable manual-tracing volumetry in 80 participants (20 with UHR, 20 with FES, and 40 matched controls). The controls constituted two groups: the first group was matched for age, sex, parental socioeconomic background, and intelligence quotient to UHR ($n = 20$); the second was matched for those to FES ($n = 20$). Compared with matched controls, the volume of the bilateral PT, but not that of the PO, was significantly reduced in the subjects with UHR and FES. The reduced right PT volume, which showed the largest effect size among regions-of-interest in the both UHR and FES groups, correlated with the severity of the positive symptoms also in the both groups. These results suggest that localized gray matter volume reductions of the bilateral PT represent a vulnerability to schizophrenia in contrast to the PO volume, which was previously found to be reduced in patients with chronic schizophrenia. The right PT might preferentially contribute to the pathogenesis of psychotic symptoms.

1. Introduction

Deficits in language-related information processing (Mitchell and Crow, 2005) and in interpersonal interactions (Lee et al., 2004) are features of the pathophysiology of schizophrenia, even in individuals at ultra-high risk for psychosis (UHR) (Yung et al., 2003; Phillips et al., 2004; Marjoram et al., 2006; Chung et al., 2008; Becker et al., 2010; Magaud et al., 2010). Broca's region and its right hemisphere counterpart in the inferior frontal gyrus (IFG), which is considered to have evolved for inter-individual communication by gestures, speech, and language (Nishitani et al., 2005), are involved in both language processing (Hagoort, 2005) and social interactions (Iacoboni and Dapretto, 2006).

The IFG is functionally and morphologically implicated to play an important role in the pathophysiology of schizophrenia. For example, previous magnetic resonance imaging (MRI) studies have revealed structural abnormalities of the IFG in patients with schizophrenia (e.g. Ananth et al., 2002; Yamasue et al., 2004; Suga et al., 2010), and subjects with UHR (Meisenzahl et al., 2008; Witthaus et al., 2009), as well as its progressive changes during the transition to the psychosis phase (Pantelis et al., 2003; Borgwardt et al., 2007).

In any anatomical evaluation of the IFG, significant individual variations in the gyral pattern of the IFG should be taken into account (Tomaiuolo et al., 1999). Changes in the shape, or displacement of structures and resolution loss could occur in the course of spatial normalization, segmentation, registration, and smoothing (Wright et al., 1999; Yucel et al., 2002; Giuliani et al., 2005; Kennedy et al., 2009) in

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computational morphometry. Therefore, computational morphometry might not detect volume changes in areas with large anatomical variability such as the IFG (Tomaiuolo et al., 1999; Eckert et al., 2005).

Broca's region and its right hemisphere counterpart in the IFG, which consists of the pars opercularis (PO), approximate Brodmann area (BA) 44, and the pars triangularis (PT), approximate BA45, are anatomically (Amunts et al., 1999) and functionally heterogeneous in language processing (Thiebaut de Schotten et al., 2005; Costafreda et al., 2006; Saur et al., 2008; Hagoort and Levelt, 2009) and in social interaction (Molnar-Szakacs et al., 2005; Iacoboni, 2009). Although our previous study suggested an importance of PT volume reduction in positive or delusional symptoms in chronic patients with schizophrenia (Suga et al., 2010), there is an insufficient evidence regarding the differential contributions of the PO and PT to the pathophysiology of schizophrenia. While gray matter volume reductions in chronic patients should reflect several different pathological effects, such as a progressive illness process, onset of illness, and a pre-acquired vulnerability to developing schizophrenia (e.g. Kasai et al., 2003; Pantelis et al., 2003; Takahashi et al., 2009), no previous study has precisely examined the morphology of IFG sub-regions in native space in subjects with UHR or first-episode schizophrenia (FES).

Thus, the present study adopted a sophisticated manual tracing volumetry approach with parcellation of the PO and PT (Suga et al., 2010; Yamasaki et al., 2010), considering anatomical variations in both UHR and FES subjects. Based on previous studies, we predicted: 1) that gray matter volume reductions in the PO and PT of patients with FES would be more localized than those in chronic patients; 2) that localized gray matter volume reductions would also be found, at least partially, in subjects with UHR; and 3) that localized gray matter volume reductions in the IFG would be associated with the severity of psychotic symptoms in subjects with UHR and FES.

2. Materials and methods

2.1. Subjects

Eighty right-handed Japanese participated in this study. Of these, 40 patients (20 FES/20 UHR), were recruited from the Department of Neuropsychiatry, The University of Tokyo Hospital, Japan. Inclusion and exclusion criteria for each group are shown in Table 1. Psychosis and UHR were diagnosed according to the Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al., 2001). To clarify the neuroanatomical change close to the onset of schizophrenia and minimize the influence of antipsychotic medication, the FES subjects were confined to those who have received antipsychotic medication for less than 16 cumulative weeks, and in whom diagnosis of schizophrenia was confirmed by a ≥6-month follow-up with the Structured Clinical Interview for DSM-IV Axis I Disorder Clinical Version (First et al., 1997b). Psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) within 7 days before and after MRI scanning. All clinical evaluations were performed by a trained psychiatrist (T.N., N.I., or Y.T.) fully trained to maintain reliability and consistency of the diagnoses (Kay et al., 1987).

Overlaps in clinical symptoms and cognitive deficits have been pointed out between schizophrenia, UHR, and autism spectrum disorders (ASD) (Barneveld et al., 2011; Solomon et al., 2011). Furthermore, ASD patients had reduced gray matter volumes in the PO and PT (Yamasaki et al., 2010). Therefore, subjects diagnosed with ASD according to the DSM-IV criteria were excluded.

Forty controls were assigned to two groups. The first group was matched to the subjects with FES (NC_{FES}, n = 20) in terms of age, sex ratio, parental socioeconomic status (SES) (Hollingshead, 1957), handedness (Oldfield, 1971), and estimated premorbid intelligence quotient (IQ) based on the Japanese version of the National Adult Reading Test (Matsuoka and Kim, 2006; Matsuoka et al., 2006; Uetsuki et al., 2006). The second control group was matched to the UHR group (NC_{UHR}, n = 20) in terms of age, sex ratio, self- and parental-SES, handedness, and estimated premorbid IQ. The controls were screened for neuropsychiatric disorders using the Structured Clinical Interview for DSM-IV Axis I Disorder Non-patient Edition (American Psychiatric Association, 1994; First et al., 1997a). The ethical committee of The University of Tokyo Hospital approved this study [No. 397 and 2226]. After a complete explanation of the study, written informed consent was obtained from every individual (Table 2).

Table 1
Inclusion and exclusion criteria.

Ultra-high risk for psychosis group
Inclusion and exclusion criteria: The Structured Interview for Prodromal Symptoms (SIPS) was employed (McGlashan et al., 2001).
First-episode schizophrenia group
Inclusion criteria: first experience of acute psychosis defined according to SIPS
AND
Antipsychotic medication for less than 16 cumulative weeks
AND
Diagnosis confirmed as schizophrenia according to DSM-IV by more than 6-months follow-up
AND
Continuous psychotic symptoms for less than 60 months
Healthy control group
Exclusion criteria
History of psychiatric disease in the subjects themselves or a family history of axis I disorder in their first-degree relatives
Exclusion criteria for all the groups
Current or past neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and substance abuse or addiction
Autism Spectrum Disorder met DSM-IV criteria

2.2. MRI acquisition

Images were acquired using a 3.0-Tesla MRI scanner (Signa; GE Healthcare, Milwaukee, Wisconsin), using the standard 8-channel head coil. For volumetric analysis, three-dimensional Fourier-transform fast-spoiled gradient recalled acquisition with steady state (3D-FSPGR) was used, because it affords excellent contrast between the gray and white matter (repetition time = 6.80 ms, echo time = 1.94 ms, flip angle = 20°, slice thickness = 1.0 mm, field of view = 240 mm, matrix = 256 × 256, number of axial slices = 176). A trained neuroradiologist found no gross abnormalities in any of the subjects. Magnetic field inhomogeneity in our scanner was monitored with daily basic quality control.

2.3.1. Definition of regions of interest

The obtained images were realigned in the coronal and axial planes using the interhemispheric fissure as a landmark, and the mid-sagittal plane was aligned to the correct head tilt using the line between the anterior and posterior commissures with SPM 8 (www.fil.ion.ucl.ac.uk/spm). The non-uniformity of intensity of all images was corrected using non-parametric non-uniform intensity normalization (N3: www.bic.mni.mcgill.ca).

The PO and PT gray matter regions of interest (ROIs) were outlined manually using a software package (3D Slicer; www.slicer.org). All manual tracing procedures were completed by a trained rater (N.I.) without knowledge of participant's information. The anatomical landmarks to delineate the PO and PT utilizing three-dimensional information were the same as those described in detail in our recent studies (Suga et al., 2010; Yamasaki et al., 2010) (Fig. 1).

2.3.2. Anatomical variations of the inferior frontal sub-regions

As in our previous studies (Suga et al., 2010; Yamasaki et al., 2010), we categorized the variants of morphologies of PO and PT each into two subtypes. In the PO, the gyral pattern consisting of

Table 2
Subject characteristics and symptom scores.

Variable	Patients (n = 40)		Controls (n = 40)		t tests	
	Mean	SD	Mean	SD	t value	P
Age (range)	23.6 (16–37)	5.4	24.6 (16–30)	3.9	−0.9	0.37
Male/female	26/14		26/14			
SES[a]	2.8	1.5	1.8	0.5	4.0	<0.001
Parental SES	2.3	0.6	2.1	0.4	1.6	0.11
IQ (JART25)[b]	104.8	12.2	106.1	9.2	−0.5	0.59
Handedness[c]	89.1	17.8	95.2	12.9	−1.8	0.084

Variable	Subjects with UHR[d] (n = 20)		Controls for Subjects with UHR[d] (n = 20)		t tests		Subjects with FES[e] (n = 20)		Controls for Subjects with FES[b] (n = 20)		t tests	
	Mean	SD	Mean	SD	t value	P	Mean	SD	Mean	SD	t value	P
Age (range)	21.4 (16–29)	3.6	22.6 (16–29)	3.8	−1.1	0.29	25.9 (17–37)	6.1	26.5 (16–30)	2.9	−0.4	0.67
Male/female	10/10		10/10				16/4		16/4			
SES[a]	2.4	1.2	1.8	0.6	1.8	0.06	3.2	1.5	1.8	0.4	3.9	<0.001
Parental SES	2.2	0.7	2.1	0.6	0.5	0.62	2.4	0.6	2.1	0.3	2.0	0.053
IQ (JART25)[b]	107.3	10.8	107.6	8.5	−0.1	0.92	102.3	13.2	104.6	9.9	−0.6	0.53
Handedness[c]	87.4	19.6	92.4	17.0	−0.9	0.39	90.8	16.1	98.0	6.2	−1.9	0.071
Neuroleptic dose[f] (mg/day)	83.5	183.4					660.2	520.5				
Neuroleptics type (atypical/typical/both/none)	6/0/1/13						14/1/5/0					
Onset of illness (years)							25.4	5.7				
Duration of illness (months)							8.9	9.7				
PANSS[g]												
Positive symptoms	13.8	3.3					16.5	4.9				
Negative symptoms	18.7	5.8					19.8	5.2				
General psychopathology	34.1	8.0					36.3	8.1				
Subtypes	APS[h]/BIPS[i]/GRD[j]/ APS + GRD = 14/1/2/3						Paranoid/ disorganized/ undifferentiated type = 16/1/3					

[a] Socioeconomic status, assessed using the Hollingshead scale. Higher scores indicate lower status.
[b] Estimated from scores on the Japanese Adult Reading Test.
[c] Assessed using the Edinburgh Inventory. >0 indicates right-handed.
[d] Ultra high-risk for psychosis.
[e] First-episode schizophrenia.
[f] Based on chlorpromazine equivalents.
[g] Positive and Negative Syndrome Scale.
[h] Attenuated Positive Symptom syndrome.
[i] Brief Intermittent Psychotic Symptom syndrome.
[j] Genetic Risk and Deterioration syndrome.

one gyrus (PO-Type I) was seen in 75 of 80 cases in the left and 73 of 80 cases in the right hemisphere. The other pattern, in which the PO was divided into two gyri (left: 5 of 80 cases, right: 7 of 80 cases), was labeled the PO-Type II. In the PT, the first PT gyral pattern (PT-Type I) was present in 39 of 80 cases in the left, and in 39 of 80 cases in the right hemisphere. In this pattern, the Sylvian fissure (SF) did not produce an apparent horizontal ramus (HRSF), and the PT and pars orbitalis appeared conjoined. In this type, the ventral boundary of the PT is the SF or a straight line extending from it. The second PT gyral pattern (PT-Type II), in which the PT and pars orbitalis were clearly distinguishable by HRSF, was observed in 41 of 80 cases in the left and in 41 of 80 cases in the right hemisphere.

2.4. Reliability of ROI definition

The inter-rater reliabilities were estimated in ten randomly selected cases by two independent raters (N.I. and M.S.) who were blinded to the group allocation. The intra-class correlation coefficients for the PO were 0.97 and 0.92 on the left and right, respectively, and those for the PT were 0.96 and 0.94, respectively. The intra-rater reliabilities were also tested by having one rater (N.I.) assess ten randomly selected cases twice with an approximately 6-months interval. The intra-class correlation coefficients for the PO were 0.99 and 0.99 on the left and right, respectively, and those for the PT were 0.98 and 0.98, respectively.

2.5. Intracranial volume

Total gray matter, white matter, and cerebrospinal fluid volumes were calculated using SPM8. Then, the intracranial volume (ICV) was calculated by summing these volumes.

2.6. Statistical analysis

Independent-sample t-tests were performed to assess volume differences between gyral pattern variations (Type I and II PO/PT patterns in each hemisphere). Diagnostic group differences in the proportions of the gyral patterns were evaluated by Fisher's exact test.

To compare volumetric measures, we employed a repeated measures analysis of variance (ANOVA) using relative volume [(absolute ROI volume)/(ICV)*100] as a dependent variable with two between-subject factors (Clinical status: patients/controls; Stage: UHR and NC_{UHR}/FES and NC_{FES}) and two within-subject factors (hemisphere: left/right; region: PO/PT). If a significant interaction between clinical status and any other factor was found, follow-up analyses using repeated measures ANOVA were performed. The threshold for statistical significance was set at $P < 0.05$.

The associations between the relative volumes of ROIs showing a significant group difference and the severity of positive, negative, and general psychopathology PANSS scores in each patient group were tested by Spearman's rank correlation. The threshold for

Table 3
Volumetric measurements.

Variables		Patients (n = 40)		Controls (n = 40)			Repeated measures ANOVA (follow-up analysis)							
		Mean	SD	Mean	SD	Effect size[a]	Clinical status		Clinical status × stage		Clinical status × hemisphere		Clinical status × stage × hemisphere	
Intracranial volume, ml		1601.2	148.1	1580.9	150.8	0.13	F	P	F	P	F	P	F	P
Pars opercularis,	LH	2.83	0.75	2.85	0.79									
Absolute volume, ml	RH	2.97	0.77	2.84	0.68									
Pars triangularis	LH	2.45	0.52	2.80	0.70									
Absolute volume, ml	RH	2.47	0.54	2.87	0.53									
Pars opercularis,	LH	0.177	0.045	0.181	0.053	−0.08	<0.01	0.95	0.63	0.43	0.40	0.53	1.14	0.29
Relative volume, %[b]	RH	0.187	0.050	0.182	0.050	0.10								
Pars triangularis	LH	0.154	0.036	0.178	0.044	−0.55	14.50	<0.01	0.08	0.78	0.13	0.72	0.28	0.60
Relative volume, %[b]	RH	0.155	0.035	0.183	0.035	−0.80								

Variables		Subjects with UHR[c] (n = 20)		Controls for subjects with UHR[c] (n = 20)			Subjects with FES[d] (n = 20)		Controls for subjects with FES[d] (n = 20)		
		Mean	SD	Mean	SD	Effect size[e]	Mean	SD	Mean	SD	Effect size[f]
Intracranial volume, ml		1580.6	160.8	1543.7	157.6	0.23	1621.8	135.1	1618.1	137.5	0.03
Pars opercularis,	LH	3.00	0.87	2.94	0.82		2.67	0.57	2.76	0.78	
Absolute volume, ml	RH	2.94	0.85	3.03	0.65		3.00	0.70	2.65	0.67	
Pars triangularis,	LH	2.55	0.56	2.93	0.67		2.35	0.48	2.67	0.72	
Absolute volume, ml	RH	2.51	0.62	2.86	0.47		2.43	0.47	2.88	0.60	
Pars opercularis,	LH	0.190	0.053	0.192	0.059	0.00	0.164	0.031	0.171	0.045	−0.22
Relative volume, %[b]	RH	0.189	0.061	0.198	0.049	−0.20	0.185	0.037	0.165	0.046	0.22
Pars triangularis,	LH	0.162	0.038	0.191	0.044	−0.68	0.146	0.031	0.165	0.042	−0.48
Relative volume, %[b]	RH	0.160	0.042	0.187	0.032	−0.94	0.150	0.028	0.178	0.039	−0.77

Abbreviations: LH/RH, Left hemisphere/right hemisphere.
[a] Effect size is calculated as: $(Mean_{patients} - Mean_{controls})/SD_{controls}$.
[b] Calculated as: absolute volume / intracranial volume × 100.
[c] Ultra high-risk for psychosis.
[d] First-episode schizophrenia.
[e] Effect size is calculated as: $(Mean_{UHR} - Mean_{controls\ for\ subjects\ with\ UHR})/SD_{controls\ for\ subjects\ with\ UHR}$.
[f] Effect size is calculated as: $(Mean_{FES} - Mean_{controls\ for\ subjects\ with\ FES})/SD_{controls\ for\ subjects\ with\ FES}$.

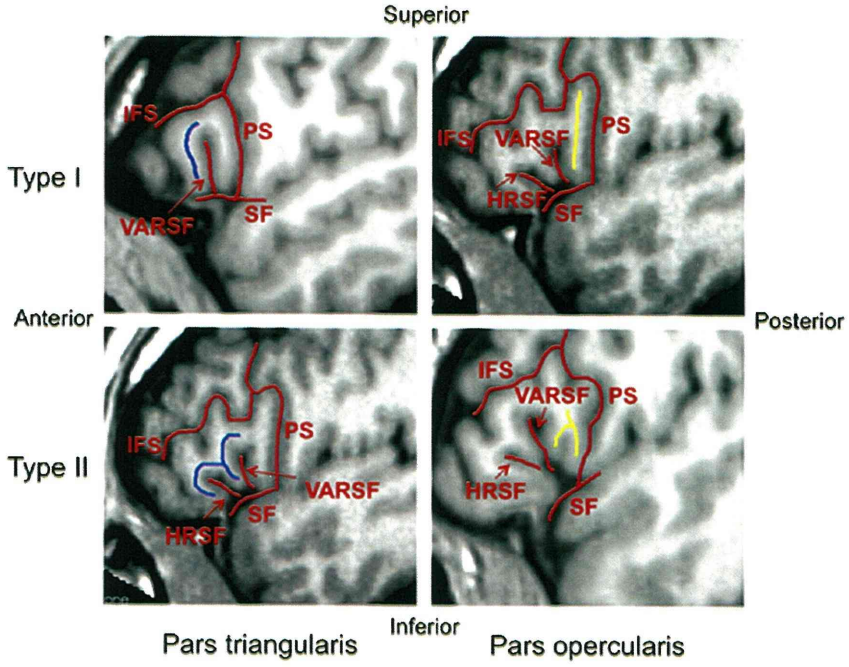

Fig. 1. Boundaries and subtypes of the regions of interest. Sagittal slices show representative samples of Type I and Type II gyrus patterns of the pars opercularis (yellow) and the pars triangularis (blue). IFS: inferior frontal sulcus; SF: Sylvian fissure; HRSF: horizontal ramus of the Sylvian fissure; VARSF: vertical ascending ramus of the Sylvian fissure; and PS: precentral sulcus.

statistical significance was again set at $P<0.05$. Additionally, the correlations between the volumes of ROIs and potential confounding factors, including age, self SES, parental SES, onset of illness, duration of illness and dose of neuroleptics, were also tested separately in each group using Spearman's rank correlation. Because correlations between these potential confounds and ROI volumes were not hypothesized in advance, the threshold for statistical significance was set at $P<0.0014$ (Bonferroni correction for 36 correlations [24 for schizophrenia group {4 ROIs × 6 clinical measures}; 12 for the control group {4 ROIs × 3 clinical measures}]).

Statistical power was estimated in a post-hoc manner using G*Power 3.1 software (Faul et al., 2007), available for free download at the website http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/download-and-register.

3. Results

3.1. Effect of the gyral pattern

The volumes of the Type II gyral pattern in the bilateral PO were significantly larger than those of the Type I pattern (left/right: $P<0.001$/$P=0.002$). In the bilateral PT, the Type I pattern was significantly larger than the Type II pattern (left/right: $P=0.006$/$P=0.011$). The anatomical variation in the subjects with FES or UHR was not statistically different from that in their matched controls in each sub-region ($P>0.4$).

3.2. Volume of ROIs

Repeated measures ANOVA showed a significant main effect of clinical status ($F[1,76]=4.33$, $P=0.041$) and a robustly significant interaction between clinical status and region ($F[1,76]=10.34$, $P=0.002$). However, no other significant interactions were found. Post-hoc repeated measures ANOVA for the PT with "clinical status" and "stage" as two between-subject factors and "hemisphere" as one within-subject factor, revealed a significant main effect of clinical status ($F[1,76]=14.50$, $P<0.001$), but no significant interactions. For the PO, there was no significant main effect of clinical status ($P=0.95$) or any interactions. Thus, although the main repeated measures ANOVA showed a significant main effect of clinical status on PO and PT volumes, the post-hoc analyses revealed that this was caused by a combination of strong effect of clinical status on PT and no effect on PO. These results demonstrated the existence of significant bilateral gray matter volume reductions in the PT, but no reductions in the PO, both in subjects with FES and those with UHR compared with their matched controls (Table 3, Fig. 2a and b).

The effect size of right PT was the largest in the subjects with FES as well as UHR. The same result was obtained when analysis of covariance using absolute volume as a dependent variable with ICV as a covariate was employed. Furthermore, to compare our new findings with previous findings in which male patients with chronic schizophrenia had smaller-than-normal PT and PO gray matter volumes bilaterally (Suga et al., 2010), analysis confined to male subjects was performed. To relate the findings to dimensions of symptoms and syndromes rather than to diagnoses, the analysis was confined to subjects with positive symptoms; UHR with Attenuated Positive Symptom syndrome and Brief Intermittent Psychotic Symptom syndrome and the paranoid type of FES, were also examined. These additional analyses reached the same conclusion: the gray matter volume reductions were localized to the PT among the PO and PT, both in subjects with FES and those with UHR.

3.3. Correlational analysis

The severity of PANSS positive symptoms was significantly associated with the smaller right PT volumes in the UHR group ($rho=-0.63$, $P=0.003$) (Fig. 3a) and marginally significantly associated with those in the FES group ($rho=-0.44$, $P=0.052$) (Fig. 3b). There were no significant correlations between left PT volumes and symptom severities.

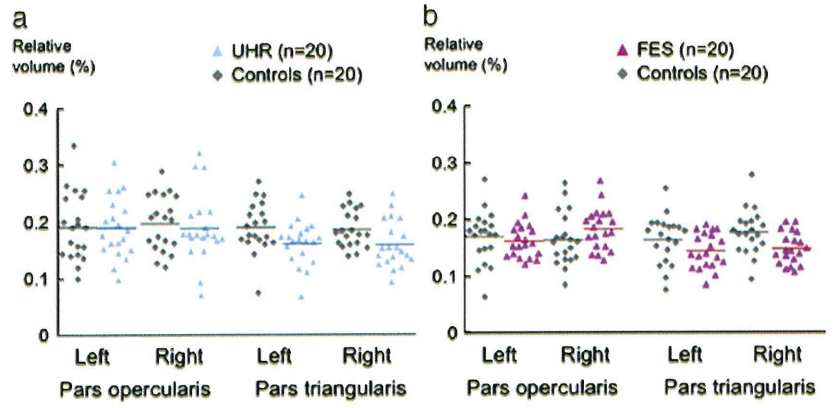

Fig. 2. Plots of gray matter volume of the regions of interest. Scatter plots show relative volumes of the pars opercularis and pars triangularis in subjects at ultra-risk for psychosis (UHR) (n = 20) and the matched controls (n = 20) (a), and in patients with first-episode schizophrenia (FES) (n = 20) and matched controls (n = 20) (b). Horizontal lines indicate the means in each group.

The smaller left PT volume in the NC_{UHR} group was significantly correlated with older age (rho = −0.695, P = 0.001). There were no other significant correlations between ROIs and potential confounding factors (corrected P > 0.5).

3.4. Post hoc power analysis

Post hoc power analysis showed the resulting power to be >0.99, for the interaction between clinical status and region in the main repeated measure ANOVA (F[1, 76] = 10.34; effect size f = 0.369), and to be 0.97 for the main effect of clinical status in follow-up repeated ANOVA results for the PT (F[1,76] = 14.50; f = 0.436). For the correlation between severity of positive symptoms and smaller right PT volumes in the UHR group, the post hoc power analysis showed the resulting power to be >0.88 based on the correlation coefficient (ρ = −0.63) and the number of subjects (n = 20). In the FES group, the post hoc power analysis for the corresponding correlation showed the resulting power to be 0.51 based on the correlation coefficient (ρ = −0.44) and the number of subjects (n = 20); the estimated sample size needed to demonstrate a significant correlation was 38 for an 80% power level at a 0.05 level of significance.

4. Discussion

To our knowledge, the present study is the first to demonstrate that both subjects with UHR and those with FES have significantly smaller-than-normal volumes of the bilateral PT, but not the PO. In particular, the volume reductions in the right PT in both UHR and FES groups, which showed the largest effect sizes among the PO and PT, were correlated with the severity of positive symptoms. It is remarkable that a similar pattern of localized gray matter volume reductions in the PT and their correlations with the positive symptoms severity were commonly found in the FES and UHR groups, because these findings were inferred on the basis of independent data acquired from independent populations.

The largest effect sizes of the right PT among localized bilateral PT volume reductions in both the UHR and FES groups were the similar to the previously found largest effect size of the right PT among the PO and PT volume reductions in patients with chronic schizophrenia (Suga et al., 2010). These findings reveal the possibility that the chronic illness process might extend the volume reduction from the PT to the PO, while the largest volume reduction in the right PT in the early phase could persist even into the chronic phase. Because

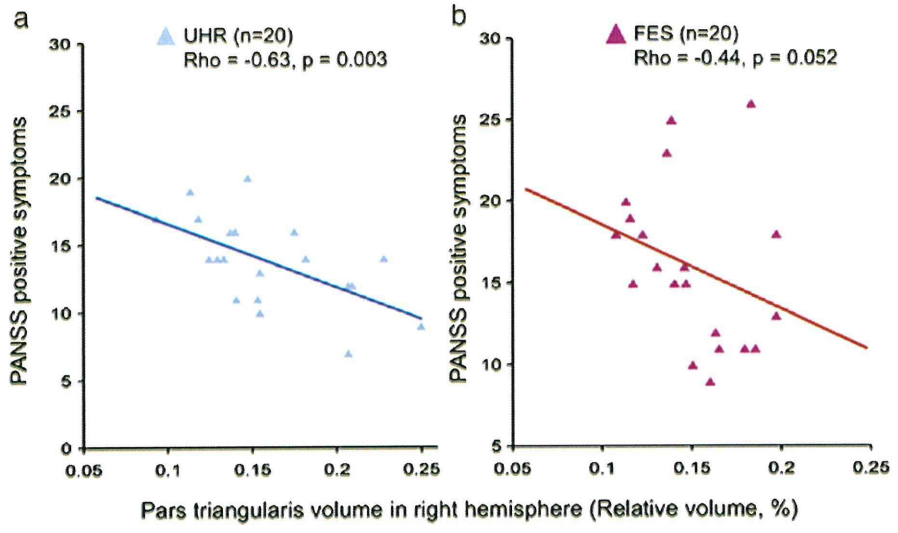

Fig. 3. Correlations between the severity of positive symptoms and the small right pars triangularis volumes. Scatterplots depicting correlations between the relative volumes of the right pars triangularis and positive symptoms scores on the Positive and Negative Syndrome Scale (PANSS) in subjects at ultra-high risk for psychosis (UHR) (rho = −0.63, P = 0.003) (a), and in the patients with first-episode schizophrenia (FES) (rho = −0.44, P = 0.052) (b).

the rate of transformation from UHR to psychosis within 12 months is relatively low (e.g. 20–40%: Yung et al., 2003; Cannon et al., 2008), the current subjects with UHR should include a majority of subjects who will not develop psychosis later. Therefore, the current findings should be interpreted with caution. However, taken together with the findings of a previous study showing gray matter density reductions in the right IFG in UHR subjects who later developed psychosis compared with those who did not (Pantelis et al., 2003), the finding of gray matter volume reductions in the PT in both UHR and FES groups could represent a marker of vulnerability to development of schizophrenia, while the finding of volume reductions in the PO could represent progression of illness after the onset of schizophrenia.

The results of the current study further showed correlations between the smaller right PT gray matter volume and more severe positive symptoms in the subjects with UHR and FES. In addition to chronic patients, in which a similar correlation between the right PT volume and the positive symptoms was found (Suga et al., 2010), the current results further indicate that the right PT plays an important role in the pathogenesis of psychotic symptoms during the early course of schizophrenia. The significance level of the correlation in the FES subjects was marginal. This might be derived from the instability of positive symptoms in the current subjects with FES at the time of introduction of antipsychotic medication (<16 weeks). Previous research has also shown a less frequently found correlation between gray matter volume and clinical symptoms in patients with FES (reviewed in McCarley et al., 1999 and Shenton et al., 2001).

Previous studies have revealed a contribution of the PT to semantic processing, and a contribution of the PO to phonological processing (reviewed in Costafreda et al., 2006; Saetrevik and Specht, 2009). Deficits in the semantic fluency test are argued to be a better trait marker for genetic liability (e.g. Chen et al., 2000; Zalla et al., 2004; Kircher et al., 2009) and clinically high risk for schizophrenia (Becker et al., 2010; Magaud et al., 2010) than those in the phonological fluency test. FES also showed the greater deficits in semantic fluency test than phonological one (Phillips et al., 2004). These previous findings seem to be consistent with the current results showing that the patients with UHR and FES show confined gray matter volume reductions in the PT, but not in the PO. The PT might be particularly involved in the formation of positive symptoms, such as delusions, through aberrant semantic processing.

The IFG has also been implicated in interpersonal interactions through imitation and observation of other's actions and emotions (Molnar-Szakacs et al., 2005; Iacoboni, 2009). A meta-analysis of the results of fMRI studies (Molnar-Szakacs et al., 2005) showed that the PO is involved in 'mirror' processing, in that it is activated during both action observation and imitation, while the PT does not exhibit mirror activity; rather, it is activated only during observation (Iacoboni, 2009). The activation of the PT during action observation and not during imitation is most readily explained by the involvement of frontal inhibitory mechanisms in suppressing movement execution during observation or motor imagery (Deiber et al., 1998). Uninhibited mirroring, caused by a disrupted PT, might be related to over-sensitivity towards the other's actions and emotions in subjects with UHR and FES.

Here we address the methodological limitations of our study. First, the present study included subjects medicated with antipsychotics. The effect of medication (Lieberman et al., 2005) on the present findings cannot be totally ruled out, although the volumes of ROIs showed no significant correlation with the doses of neuroleptics. Second, because the UHR group should contain both subjects who will develop schizophrenia later and those who will not, whether reduced PT volume predicts onset of schizophrenia could not be readily concluded by our cross-sectional study design. Third, the sample size of each group (n = 20) was relatively small compared with those in earlier studies examining UHR or FES (or first episode psychosis) subjects with manual tracing volumetry (e.g. n = 22–162, Velakoulis et al., 2006; Takahashi et al., 2009; Buehlmann et al., 2010) although the present study processed sufficient statistical power by employing repeated measure ANOVA with two between-subjects factors in the whole sample (n = 80) as the main analysis. There remains the possibility that we could not detect a correlation between symptom severity and brain volume in FES subjects owing to the small sample size, although the difficulty of detecting a correlation between symptom severity and gray matter volume reduction has been suggested by previous studies (reviewed in McCarley et al., 1999 and Shenton et al., 2001). Therefore, future studies should examine the behavioral correlates of reduced gray matter volume in the PT in FES patients with a sufficient sample size.

Overall, considered together with our recent findings in chronic schizophrenia patients (Suga et al., 2010), the present results indicate that the gray matter volume reductions in the PT relate to the pathogenesis of positive symptoms and represent a means of determining the propensity for development of schizophrenia, while gray matter volume reductions in the PO represent a marker for illness progression.

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Contributors

N.I. and H.Y. contributed to project management and wrote the manuscript. T.N. and Y.T. helped clinical evaluations and the recruitment of the participants. Y.S., S.K., and H.I. made effort for the recruitment of the participants. N.Y. advised and supported MR imaging processing. M.M., M.K., W.G., H.S., H.T., and O.A supervised MR imaging acquisitions and evaluated all of the acquired images. M.S. constructed the manual tracing methodology of the inferior frontal sub-regions and spared a lot of time for the assessment of inter-rater reliability. K.K. and H.Y. coordinated the entire research design and took responsibility for the management of this study. All authors contributed to the critical revision and final approval of the manuscript.

Conflict of interest

All of the authors reported no biomedical financial interests or potential conflicts of interest.

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