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# Reduced Hippocampal Subfield Volume in Schizophrenia and Clinical High-Risk State for Psychosis

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Magnetic resonance imaging (MRI) studies in schizophrenia demonstrated volume reduction in hippocampal subfields divided on the basis of specific cytoarchitecture and function. However, it remains unclear whether this abnormality exists prior to the onset of psychosis and differs across illness stages. MRI (3 T) scans were obtained from 77 patients with schizophrenia, including 24 recent-onset and 40 chronic patients, 51 individuals with an at-risk mental state (ARMS) (of whom 5 subsequently developed psychosis within the follow-up period), and 87 healthy controls. Using FreeSurfer software, hippocampal subfield volumes were measured and compared across the groups. Both schizophrenia and ARMS groups exhibited significantly smaller volumes for the bilateral Cornu Ammonis 1 area, left hippocampal tail, and right molecular layer of the hippocampus than the healthy control group. Within the schizophrenia group, chronic patients exhibited a significantly smaller volume for the left hippocampal tail than recent-onset patients. The left hippocampal tail volume was positively correlated with onset age, and negatively correlated with duration of psychosis and duration of medication in the schizophrenia group. Reduced hippocampal subfield volumes observed in both schizophrenia and ARMS groups may represent a common biotype associated with psychosis vulnerability. Volumetric changes of the left hippocampal tail may also suggest ongoing atrophy after the onset of schizophrenia.

**Keywords: hippocampal subfield, hippocampal tail, at-risk mental state, schizophrenia, volumetry, magnetic resonance imaging, CA1, molecular layer of the hippocampus**

## INTRODUCTION

There is increasing evidence supporting that abnormality of the hippocampus, which subserves a range of roles in learning, memory, and emotional regulation (1, 2), functions in the symptomatology and cognitive impairment of schizophrenia (3, 4). Importantly, the hippocampus is not a uniform structure but rather an aggregate of anatomically and functionally different substructures [e.g., the Cornu Ammonis (CA), dentate gyrus (DG), molecular layers, and subiculum; (5)]. Based on the notion of differently affected hippocampal subfields in schizophrenia

(6–8), an etiological hypothesis claimed that exaggerated pattern completion induced by aberrant dentate-to-CA3 connections generated psychotic associations (9), whereas another hypothesis argued that hippocampal hypermetabolism originating from CA1 was related to acquired psychotic symptoms and mnemonic interference (10). However, much of the hippocampus-mediated mechanism involved in the onset and progress of psychosis remains unknown. Thus, examining functional or structural abnormalities of the hippocampal subfields, and assessing their potential roles as psychosis biotype constructs may be of interest (11).

A hippocampal volume deficit is among the most robust magnetic resonance imaging (MRI) findings in schizophrenia patients (12–14). However, it remains unclear when such hippocampal abnormalities occur, i.e., either before or after onset, or both, due to inconsistent findings in individuals with an at-risk mental state (ARMS) (15) [reduced hippocampal volume (16–18) or no differences (19–24)] and in patients with schizophrenia [progressive volume loss (19, 25, 26) or no atrophy over time (27–30)]. These discrepancies among previous studies may be partly explained by the possibility that hippocampal reduction exists only in specific subfields (16, 21). However, limited studies of hippocampal subfields reported mixed results [reviewed by Haukvik et al. (31) and Hu et al. (32)], with schizophrenia patients having prominent volume reduction in the CA1 (33) or more widespread reductions in the CA2/3, CA4/DG, presubiculum, subiculum, and CA1 (34, 35). Similar findings were reported in a few studies examining hippocampal subfield volumes in ARMS individuals (23, 36). Hippocampal subfield segmentation on the MRI methodology is under development (37), which may partly explain the heterogeneity of the results. Although diverse relationships between severe psychotic symptoms (34, 38, 39) or poor cognitive performance (34, 36, 40) and volume reductions in CA4/DG, CA2/3, CA1, and subiculum has been reported in schizophrenia patients, it remains unknown whether hippocampal abnormalities are related to subclinical psychotic or cognitive manifestation in ARMS individuals. Further studies are required to examine the hippocampal subfield volume changes in psychotic disorders using a more comprehensive and fine-grained segmentation protocol, ideally in multiple disease phases, including the prodromal stage.

This MRI study investigated volumetric alterations of the hippocampal subfield and their relevance to psychotic symptom or cognitive function in schizophrenia patients, including recent-onset and chronic patients, and ARMS individuals compared with healthy controls. We applied a novel segmentation algorithm using an *ex vivo* atlas (41), which was reported to have superior compatibility with existing histopathological information to the conventional one using only an *in vivo* atlas (42, 43), in order to label the hippocampal subfields. Based on recent MRI findings (23, 33, 36, 40), we predicted that both schizophrenia and ARMS subjects have reduced volumes of the specific hippocampal subfields, but that disease chronicity and/or medication may affect the findings. As hippocampal subfield atrophy and clinical symptoms or socio-cognitive deficits in ARMS were reported to be less severe compared to schizophrenia (36, 44), we also predicted their associations predominantly in schizophrenia.

# MATERIALS AND METHODS

## Study Participants

Seventy-seven patients with schizophrenia, 51 individuals with ARMS, and 87 healthy control subjects were included in the current study (**Table 1**). Between December 2013 and August 2019, the study participants were recruited and examined at the clinics of the Department of Neuropsychiatry, Toyama University Hospital.

The schizophrenia patients were assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition (SCID-I/P) (45) and a detailed chart review, and fulfilled both the DSM-IV-TR (46) and DSM-5 (47) criteria. Recent-onset schizophrenia (ROSz) patients were defined by a duration of psychosis <1 year ($n = 24$, age = 24.5 ± 10.1 years, duration of psychosis = 0.4 ± 0.2 years) (48, 49), whereas chronic schizophrenia patients were defined as those with a duration of psychosis >3 years ($n = 40$, age = 32.4 ± 8.5 years, duration of psychosis = 9.9 ± 6.4 years) (50). As an additional analysis, we also defined the chronic schizophrenia patients as those with a duration of psychosis > 10 years ($n = 16$, age = 36.1 ± 7.2 years, duration of psychosis = 16.2 ± 5.6 years) to limit them to more chronic patients. Sixty-five patients with schizophrenia were receiving antipsychotics at the time of MRI. They were treated with risperidone ($n = 7$), paliperidone ($n = 4$), olanzapine ($n = 25$), quetiapine ($n = 4$), aripiprazole ($n = 17$), perospirone ($n = 6$), blonanserin ($n = 9$), zotepine ($n = 1$), clozapine ($n = 1$), haloperidol ($n = 2$), levomepromazine ($n = 6$), and/or fluphenazine ($n = 1$).

Through a local early intervention service in Toyama (51), ARMS individuals who were diagnosed by the Japanese version of the Comprehensive Assessment of At Risk Mental States (CAARMS) (15, 52) were recruited. All 51 ARMS individuals didn't exceed the threshold for psychosis on the CAARMS at baseline (**Table 1**). The ARMS individuals were prospectively followed (mean = 3.7 years, $SD = 3.0$ years), and subdivided into five individuals (9.6%) who later developed psychosis (ARMS-P) and 28 who did not develop psychosis during clinical follow-up of at least 2 years (ARMS-NP). Based on the DSM-IV-TR criteria, all psychotic disorders in ARMS-P subjects were diagnosed as schizophrenia. Regarding psychiatric comorbidities, ARMS subjects were also diagnosed with pervasive developmental disorders (PDD) ($n = 5$), attention-deficit and disruptive behavior disorders ($n = 1$), depressive disorders ($n = 6$), anxiety disorders ($n = 8$), dissociative disorders ($n = 1$), eating disorders ($n = 1$), adjustment disorders ($n = 9$), schizotypal personality disorders ($n = 3$), or avoidant personality disorders ($n = 1$). At the timing of MRI, 11 subjects (21.6%) were receiving a low dosage of antipsychotics for their severe psychiatric conditions in accordance with the clinical guidelines for early psychosis (53). Simultaneously, 5 subjects (9.8%) were taking antidepressants (imipramine equivalent doses = 112.5 ± 65.0 mg/day), and 14 subjects

**TABLE 1 |** Demographic and clinical data of the healthy comparison (HC), at-risk mental state (ARMS), and schizophrenia (Sz) groups.

| | HC | ARMS | Sz | Statistics |
|---|---|---|---|---|
| | (*n* = 87) | (*n* = 51) | (*n* = 77) | |
| Sex, male/female (*n*) | 46/41 | 29/22 | 39/38 | Chi-square = 0.48, $p = 0.788$ |
| Age (years) | 26.3 ± 3.9 | 18.3 ± 4.2 | 28.8 ± 9.4 | $F_{(2, 214)} = 41.59$, $p < 0.001$; ARMS < HC < Sz |
| Height (cm) | 165.7 ± 8.3 | 164.1 ± 8.0 | 164.3 ± 8.8 | $F_{(2, 214)} = 0.77$, $p = 0.465$ |
| Intracranial volume (ml) | 1553 ± 126 | 1485 ± 144 | 1501 ± 168 | $F_{(2, 214)} = 3.74$, $p = 0.025$[a]; ARMS < HC, Sz |
| JART-IQ[b] | 110.0 ± 6.8 | 97.3 ± 9.3 | 101.2 ± 8.7 | $F_{(2, 181)} = 43.06$, $p < 0.001$; ARMS < Sz < HC |
| Handedness (right/left/mixed) | 60/8/19 | 31/3/17 | 63/2/12 | Chi-square = 9.33, $p = 0.053$ |
| Socioeconomic status | 6.3 ± 0.8 | 3.1 ± 1.4 | 4.4 ± 1.3 | $F_{(2, 214)} = 131.15$, $p < 0.001$; ARMS < Sz < HC |
| Parental socioeconomic status[c] | 5.9 ± 0.9 | 4.9 ± 0.9 | 4.9 ± 1.3 | $F_{(2, 213)} = 21.36$, $p < 0.001$; ARMS, Sz < HC |
| Age at onset (years) | | | 22.8 ± 8.1 | |
| Duration of psychosis (years) | | | 5.6 ± 6.5 | |
| Medication dose (HPD equivalent, mg/day) | | 3.0 ± 3.2 (*n* = 11) | 10.6 ± 8.3 (*n* = 65) | $F_{(1, 75)} = 8.73$, $p = 0.004$; ARMS < Sz |
| Medication type (atypical/typical/mixed) | | 10/1/0 | 56/0/9 | Chi-square = 139.39, $p < 0.001$ |
| Duration of medication (years) | | 0.6 ± 0.8 (*n* = 6) | 6.1 ± 6.8 (*n* = 56) | $F_{(1, 61)} = 3.79$, $p = 0.056$ |
| PANSS positive | | 12.3 ± 3.4 | 15.5 ±6.3 | $F_{(1, 124)} = 10.47$, $p = 0.002$; ARMS < Sz |
| PANSS negative | | 16.4 ± 6.9 | 18.2 ± 7.5 | $F_{(1, 124)} = 1.98$, $p = 0.162$ |
| PANSS general | | 31.9 ± 7.9 | 35.0 ± 11.5 | $F_{(1, 124)} = 2.71$, $p = 0.102$ |
| **CAARMS subscale scores** | | | | |
| Unusual thought global rating scale | | 3.6 ± 1.4 | | |
| Unusual thought frequency scale | | 3.6 ± 1.9 | | |
| Non-Bizarre ideas global rating scale | | 3.9 ± 1.1 | | |
| Non-Bizarre ideas frequency scale | | 4.4 ± 1.3 | | |
| Perceptual abnormalities global rating scale | | 3.1 ± 1.6 | | |
| Perceptual abnormalities frequency scale | | 3.1 ± 1.9 | | |
| Disorganized speech global rating scale | | 2.5 ± 1.3 | | |
| Disorganized speech frequency scale | | 4.1 ± 2.4 | | |
| **BACS subdomain z-scores** | | | | |
| Verbal memory | | −0.7 ± 1.4 | −1.3 ± 1.4 | $F_{(1, 112)} = 6.05$, $p = 0.015$; Sz < ARMS |
| Working memory | | −0.8 ± 1.3 | −0.9 ± 1.3 | $F_{(1, 112)} = 0.16$, $p = 0.692$ |
| Motor function | | −0.9 ± 1.3 | −2.0 ± 1.5 | $F_{(1, 112)} = 19.59$, $p < 0.001$; Sz < ARMS |
| Verbal fluency | | −0.9 ± 1.4 | −0.9 ± 1.1 | $F_{(1, 112)} = 0.024$, $p = 0.877$ |
| Attention and processing speed | | −0.3 ± 1.4 | −1.2 ± 1.3 | $F_{(1, 112)} = 12.03$, $p < 0.001$; Sz < ARMS |
| Executive function | | −0.4 ± 1.3 | −0.7 ± 1.8 | $F_{(1, 112)} = 0.87$, $p = 0.354$ |
| BACS mean z-score | | −0.7 ± 1.0 | −1.2 ± 1.0 | $F_{(1, 112)} = 7.13$, $p = 0.009$; Sz < ARMS |
| SCoRS global rating score | | 5.3 ± 2.2 | 5.0 ± 2.5 | $F_{(1, 102)} = 0.43$, $p = 0.516$ |
| SOFAS | | 50.2 ± 10.5 | 47.3 ± 14.3 | $F_{(1, 87)} = 1.19$, $p = 0.279$ |

*Values represent the mean ± SD unless otherwise stated.*

*ARMS, At-Risk Mental State; BACS, Brief Assessment of Cognition in Schizophrenia; CAARMS, Comprehensive Assessment of At-Risk Mental State; IQ, Intelligence Quotient; JART, Japanese version of National Adult Reading Test; HC, healthy controls; HPD, haloperidol; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; Sz, schizophrenia.*

[a]*Age was used as a covariate.*

[b]*Data missing for 33 subjects.*

[c]*Data missing for one subject.*

(27.5%) were taking anxiolytics (diazepam equivalent doses = 5.1 ± 2.2 mg/day). Omega-3 fatty acids were not used in any subjects.

Healthy control subjects with no personal or family (first-degree relatives) history of psychiatric diseases who were screened by the SCID-I Non-patient Edition (45) were recruited from hospital staff, University students, and members of the local community.

All participants in the present study were physically healthy at the time of MRI and had no lifetime history of serious head trauma, neurological illness, substance abuse, steroid use, or other serious physical diseases. One hundred and sixty-one of the 216 subjects were also included in our previous study that investigated subregional volumes of the thalamus and basal ganglia in schizophrenia and ARMS (54). The Committee on Medical Ethics of Toyama University approved

this study. Written informed consent was received from all study participants. If the participants were under the age of 20, their parent or guardian also provided written consent.

## Clinical Assessment

Clinical symptoms of the schizophrenia and ARMS subjects were rated by the Positive and Negative Syndrome Scale (PANSS) (55), whose scores consisted of the positive items, negative items, and general psychopathology. Cognitive assessments were conducted using the Brief Assessment of Cognition in Schizophrenia (BACS) (56, 57). The BACS scores from their six subdomains (verbal memory, working memory, motor speed, verbal fluency, attention, and executive function) were standardized by calculating z-scores, where the mean score of the healthy Japanese was set to zero and the standard deviation was set to one (58). The Schizophrenia Cognition Rating Scale (SCoRS) (59–61) were also conducted to measure the cognitive abilities related to daily-living functioning or functional capacity. Among 20 items of the SCoRS, global rating scale (range 1–10, higher ratings mean greater impairment in daily living skills) was adapted as a representative value. Social functioning was evaluated by the Social and Occupational Functioning Assessment Scale (SOFAS) (62), whose score (range 0–100, higher ratings mean better functioning) corresponded to the social functioning domain of the Global Assessment of Functioning Scale in the DSM-IV-TR (46). All assessments were administered by experienced psychiatrists and trained psychologists.

## MRI

Study participants were scanned using a 3-T Magnetom Verio (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional magnetization-prepared rapid gradient echo (MPRAGE) sequence yielding 176 contiguous T1-weighted slices of 1.2-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time = 2,300 ms, echo time = 2.9 ms, flip angle = 9°, field of view = 256 mm, and matrix size = 256 × 256. The voxel size was 1.0 × 1.0 × 1.2 mm.

## Measurement of Hippocampal Subfields

Preprocessing of the T1-weighted images, including the correction for intensity non-uniformity in MRI data (63), was performed using the FreeSurfer pipeline (version 6.0, http://surfer.nmr.mgh.harvard.edu) (64, 65). One trained researcher (RY) blinded to the subjects' identities visually inspected all reconstructed images, and manually edited them to improve their subcortical and temporolimbic segmentations. The hippocampal region was automatically segmented into 12 different subfields using a new algorithm, which was based on a computational atlas assembled from *ex vivo* MRI data of post-mortem medial temporal tissue and *in vivo* MRI data informing about neighboring extrahippocampal structures (41). All subfield outputs were also visually inspected to ensure no robust mislabeling. We measured the intracranial volume (ICV), and volume of the entire hippocampus and 12 hippocampal subfields: hippocampal tail, subiculum, CA1, hippocampal fissure, presubiculum, parasubiculum, molecular layer hippocampus (HP), granule cell and molecular layer of the dentate gyrus (GC-ML-DG), CA3, CA4, fimbria, and hippocampus-amygdala-transition-area (HATA).

## Statistical Analysis

Clinical and demographic differences among groups were examined by one-way analysis of variance (ANOVA) or chi-square test.

Absolute regional volumes were analyzed using the repeated measures multivariate analysis of variance (MANCOVA), with age and ICV as covariates, diagnosis (e.g., healthy controls vs. ARMS vs. schizophrenia, ARMS-P vs. ARMS-NP, ROSz vs. chronic schizophrenia, and ARMS vs. ROSz vs. chronic schizophrenia) and sex as between-subject factors, and hemisphere and hippocampal subfields (12 regions) as within-subject variables. We assessed the effects of subfield by lower order MANCOVA only when we detected significant diagnosis-by-subfield-by-hemisphere interactions (**Table 2**) in order to prevent possible type I errors. *Post-hoc* Newman-Keuls tests were employed to follow-up the significant main effects or interactions.

Test-retest reliability of FreeSurfer automated hippocampal subfield segmentation has been established using 3T-MRI data (66, 67). For validation analyses, however, we also combined parts of the subfields to set up the merged hippocampal subfields, such as CA1, subiculum$_{combined}$ (subiculum + presubiculum + parasubiculum), and other (GC-ML-DG + CA3 + CA4) subfields on the basis of previous studies (68, 69). Using the same repeated measures MANCOVA model, absolute regional volumes of these merged subfields were analyzed among the schizophrenia, ARMS, and control groups.

Relationships between the absolute volume of the hippocampal subfields with significant group differences (i.e., hippocampal tail, subiculum, CA1, and molecular layer HP; **Table 2**) and clinical or socio-cognitive variables [e.g., age at onset, duration of psychosis, medication dose, duration of medication, PANSS (positive, negative, and general), BACS (mean z-scores), SCoRS global rating score, and SOFAS] in the schizophrenia and ARMS groups were explored by Pearson's partial correlation coefficients controlled for age, sex, and ICV.

The significance threshold was set at $p < 0.05$ (two-sided). For correlation analyses, a Bonferroni correction was applied to correct for multiple comparisons.

# RESULTS

## Sample Characteristics

Demographic and clinical characteristics of the sample are summarized in **Table 1**. Groups were matched for sex, height, and handedness, but there were significant differences in age, ICV, premorbid Intelligence Quotient, and personal/parental socioeconomic status. The schizophrenia patients were characterized by higher PANSS positive scores, lower BACS measures, and greater amounts of antipsychotics than ARMS individuals.

**TABLE 2 |** Absolute volume of the hippocampal subfields in the HC, ARMS, and Sz groups.

| Region of Interest ($mm^3$) | HC ($n = 87$) | ARMS ($n = 51$) | Sz ($n = 77$) | Multivariate analysis of covariates | | *Post-hoc* tests | |
|---|---|---|---|---|---|---|---|
| | (Male 46, Female 41) | (Male 29, Female 22) | (Male 39, Female 38) | Diagnosis × Subfield × Hemisphere | | Sz vs. HC | ARMS vs. HC |
| | Mean ± SD | Mean ± SD | Mean ± SD | $F_{(22,2299)}$ | *P* | *P* | *P* |
| Entire hippocampus | | | | 1.79 | **0.01** | | |
| Left | 3523.5 ± 310.5 | 3403.5 ± 340.3 | 3378.0 ± 312.2 | | | | |
| Right | 3615.6 ± 343.7 | 3429.0 ± 312.8 | 3495.5 ± 361.8 | | | | |
| Hippocampal tail | | | | – | – | | |
| Left | 551.8 ± 65.9 | 522.7 ± 53.6 | 520.0 ± 58.3 | | | **$1.76 \times 10^{-5}$** | **$5.67 \times 10^{-5}$** |
| Right | 570.6 ± 70.5 | 542.7 ± 67.6 | 554.6 ± 55.6 | | | 0.08 | **$5.51 \times 10^{-4}$** |
| Subiculum | | | | – | – | | |
| Left | 445.5 ± 47.9 | 430.3 ± 50.8 | 432.3 ± 47.0 | | | 0.12 | 0.10 |
| Right | 454.8 ± 48.3 | 424.4 ± 48.4 | 439.9 ± 50.1 | | | 0.06 | **$8.30 \times 10^{-5}$** |
| CA1 | | | | – | – | | |
| Left | 635.9 ± 72.4 | 619.8 ± 69.5 | 612.3 ± 63.5 | | | **$1.15 \times 10^{-3}$** | **$1.54 \times 10^{-2}$** |
| Right | 676.9 ± 92.2 | 643.5 ± 73.5 | 652.5 ± 75.5 | | | **$2.40 \times 10^{-4}$** | **$2.30 \times 10^{-5}$** |
| Hippocampal fissure | | | | | | | |
| Left | 150.5 ± 25.4 | 154.0 ± 29.5 | 153.1 ± 26.6 | | | 0.70 | 0.86 |
| Right | 144.8 ± 21.8 | 143.5 ± 23.1 | 154.2 ± 26.8 | | | 0.62 | 0.85 |
| Presubiculum | | | | – | – | | |
| Left | 320.1 ± 33.6 | 311.4 ± 41.0 | 306.3 ± 39.0 | | | 0.23 | 0.38 |
| Right | 313.1 ± 35.5 | 296.4 ± 34.6 | 299.8 ± 42.2 | | | 0.34 | 0.19 |
| Parasubiculum | | | | – | – | | |
| Left | 65.2 ± 10.1 | 63.6 ± 9.2 | 60.4 ± 9.9 | | | 0.98 | 0.82 |
| Right | 61.3 ± 9.8 | 59.8 ± 8.2 | 57.3 ± 9.6 | | | 1.00 | 1.00 |
| Molecular layer HP | | | | – | – | | |
| Left | 576.1 ± 56.0 | 558.4 ± 59.7 | 552.7 ± 54.8 | | | **$7.77 \times 10^{-3}$** | 0.06 |
| Right | 597.6 ± 65.6 | 563.5 ± 54.8 | 575.5 ± 60.9 | | | **$2.56 \times 10^{-3}$** | **$1.97 \times 10^{-5}$** |
| GC-ML-DG | | | | – | – | | |
| Left | 303.5 ± 33.9 | 295.3 ± 37.4 | 291.6 ± 35.6 | | | 0.55 | 0.73 |
| Right | 307.8 ± 36.0 | 292.1 ± 30.4 | 298.2 ± 40.6 | | | 0.60 | 0.27 |
| CA3 | | | | – | – | | |
| Left | 200.4 ± 25.8 | 195.4 ± 27.1 | 195.4 ± 26.3 | | | 0.88 | 0.74 |
| Right | 207.4 ± 29.6 | 198.8 ± 26.8 | 206.2 ± 33.4 | | | 0.85 | 0.57 |
| CA4 | | | | – | – | | |
| Left | 260.1 ± 29.0 | 253.2 ± 32.7 | 249.0 ± 29.1 | | | 0.34 | 0.55 |
| Right | 260.4 ± 30.0 | 248.4 ± 26.3 | 253.8 ± 34.9 | | | 0.58 | 0.46 |
| Fimbria | | | | – | – | | |
| Left | 102.8 ± 16.8 | 94.1 ± 16.8 | 99.5 ± 20.9 | | | 0.62 | 0.69 |
| Right | 103.5 ± 18.1 | 96.3 ± 17.2 | 97.9 ± 22.5 | | | 0.84 | 0.82 |
| HATA | | | | – | – | | |
| Left | 62.2 ± 7.5 | 59.2 ± 6.0 | 58.5 ± 8.4 | | | 1.00 | 1.00 |
| Right | 62.3 ± 7.4 | 59.4 ± 8.0 | 59.9 ± 9.2 | | | 1.00 | 1.00 |

*ARMS, at-risk mental state; CA, Cornu Ammonis; GC-ML-DG, granule cell and molecular layer of the dentate gyrus; HATA, hippocampus-amygdala-transition-area; HC, healthy controls; HP, hippocampus; Sz, schizophrenia.*
*Bold font indicates statistical significance.*

## Volumetric Analyses

On comparison among the schizophrenia, ARMS, and control groups, MANCOVA of the hippocampal volume revealed a significant diagnosis-by-subfield-by-hemisphere interaction. We therefore separately evaluated the group differences in hippocampal subfields for each hemisphere. Compared with controls, the schizophrenia group had a smaller volume in the bilateral CA1, bilateral molecular layer HP, and left hippocampal

tail, and the ARMS group had a smaller volume in the bilateral hippocampal tail, bilateral CA1, right subiculum, and right molecular layer HP (**Table 2**). However, the hippocampal volumes did not differ between the schizophrenia and ARMS groups. ARMS subsample without comorbid PDD diagnosis ($n = 46$) also exhibited a smaller volume in the hippocampal tail ($p = 3.20 \times 10^{-5}$ for left side and $p = 6.78 \times 10^{-5}$ for right side), CA1 ($p = 2.29 \times 10^{-2}$ for left side and $p = 9.54 \times 10^{-6}$ for right side), and subiculum ($p = 3.02 \times 10^{-2}$ for left side and $p = 6.69 \times 10^{-5}$ for right side) bilaterally, as well as in the right molecular layer HP ($p = 1.15 \times 10^{-5}$) compared with controls (**Supplementary Table 1**).

There were no significant differences in the hippocampal volumes between the ARMS-P and -NP groups (**Supplementary Table 2**).

On comparison between the ROSz and chronic schizophrenia groups, a significant diagnosis-by-subfield-by-hemisphere interaction was observed by MANCOVA [$F_{(11, 660)} = 3.58$, $p < 0.001$]. *Post-hoc* analyses demonstrated that the left hippocampal tail was significantly reduced in chronic schizophrenia patients compared with ROSz patients ($p = 1.58 \times 10^{-4}$) (**Supplementary Table 3**). Similarly, re-defined chronic schizophrenia patients (duration of psychosis >10 years) exhibited a significant volume reduction only in the left hippocampal tail compared with ROSz patients ($p = 2.42 \times 10^{-4}$) (**Supplementary Table 4**).

Direct comparison among the ARMS, ROSz, and chronic schizophrenia groups showed a significant diagnosis-by-subfield-by-hemisphere interaction [$F_{(22, 1199)} = 3.19$, $p < 0.001$], and the *post-hoc* tests indicated that the left hippocampal tail was significantly reduced in chronic schizophrenia group compared with ROSz ($p = 2.82 \times 10^{-5}$) and ARMS ($p = 8.28 \times 10^{-3}$) groups, as well as in ARMS group compared with ROSz ($p = 3.81 \times 10^{-2}$) group (**Supplementary Table 5**).

For the analysis of merged hippocampal subfields, a significant diagnosis-by-hemisphere interaction was observed by MANCOVA [$F_{(2, 209)} = 5.12$, $p = 0.01$]. *Post-hoc* analyses demonstrated that sum of the merged hippocampal subfield of the right hemisphere was significantly reduced in ARMS individuals compared with controls ($p = 5.80 \times 10^{-3}$) (**Supplementary Table 6**). However, MANCOVA showed no significant interactions involving diagnosis-by-subfield, supporting the utility of more detailed subfield analyses.

The results of these comparisons remained essentially the same even when medication (dosage and duration) was included as a covariate.

## Correlation Analyses

The left hippocampal tail volume was positively correlated with onset age and negatively correlated with duration of psychosis in patients with schizophrenia (**Figure 1**, **Table 3**). In the schizophrenia group, volume reduction of the left hippocampal tail was significantly associated with long-term medication use, whereas the hippocampal subfield volume was not associated with antipsychotic medication dosage (**Figure 1**, **Table 3**). In ARMS individuals, we found no significant relationship between the hippocampal volume and clinical or socio-cognitive variables.

# DISCUSSION

In the present MRI study, we have investigated hippocampal subfield volumes based on a reliable *ex vivo* atlas cross-sectionally across multiple stages of psychosis. The schizophrenia and ARMS groups had significantly smaller volumes of the CA1, hippocampal tail, and molecular layer HP than healthy controls, suggesting that hippocampal abnormalities in these specific subfields represent a static vulnerability marker of psychosis. On the other hand, the volume loss in the left hippocampal tail preferentially observed in the chronic stage of psychosis, which was related to early onset age and long-term duration of psychosis, may reflect a regional progressive pathological process after onset.

Our finding of reduced hippocampal volume, especially in the CA1, hippocampal tail, and molecular layer HP, was partly consistent with four previous studies (23, 33, 43, 70) in psychotic disorders that assessed hippocampal subfields using a recent version of segmentation by Iglesias et al. (41). On the other hand, previous studies (34, 35, 39) mainly employing an earlier version of segmentation by Leemput et al. (42) reported widespread volume reductions centered on the CA2/3, CA4/DG, and subiculum. Different segmentation methods among the studies may be partly responsible for these discrepancies; the segmentation protocol by Leemput et al. (42) may have underestimated CA1 volumes and overestimated CA2/3 or subiculum volumes compared with manual demarcation (71, 72). In addition, although the relationship between hippocampal subfield morphology and antipsychotic medication has not been well-documented (31), we cannot exclude the potential confounding effects of antipsychotic medication on the results, in consideration of experimental findings of alterations in hippocampal neurogenesis (73) and hippocampal volumes (74) after antipsychotic treatment. Indeed, we noted a relationship between the hippocampal tail and medication duration, but not medication dosage. The discrepancy might be partly due to the inseparable effects of duration of medication and psychosis, or to the opposite effects of medication dosage on hippocampal anatomy in acute and long-term treatment (75). As the group difference remained significant even when we added medication duration and dosage as covariates in the analytical model, reduced volume of the hippocampal subfields in our schizophrenia cohort cannot be explained only by antipsychotic drug action. Although we failed to detect a significant relationship between hippocampus atrophy and clinical symptoms or cognitive deficits, further studies are required to clarify each specialized role of functional/structural abnormalities of the CA1, molecular layer HP, and hippocampal tail in the pathophysiology of schizophrenia.

Partially consistent with a previous study of an ARMS cohort (23, 36), clinically high-risk subjects for psychosis demonstrated reduced volumes in the CA1, molecular layer HP, hippocampal tail, and subiculum, most of which were also

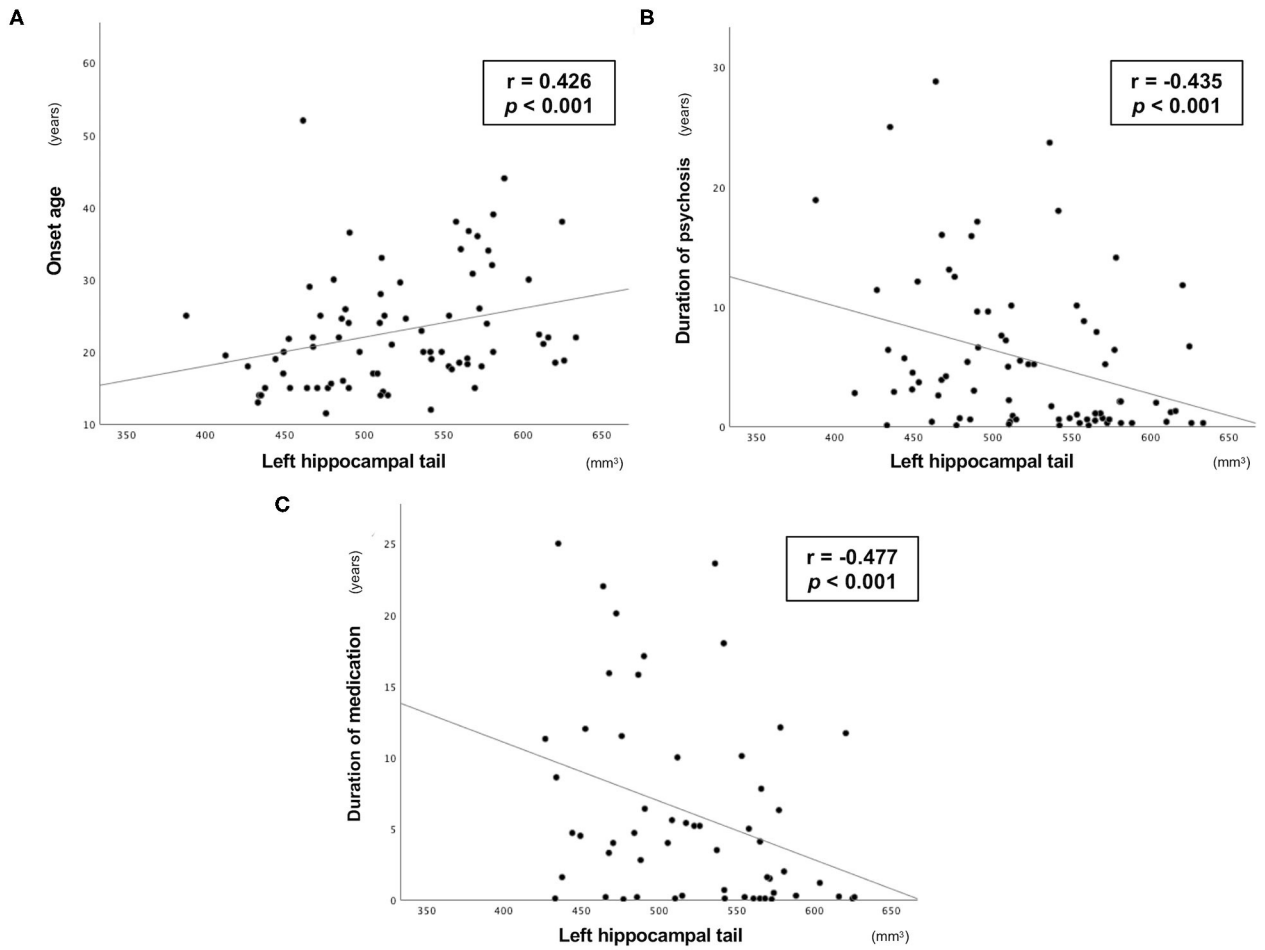


**FIGURE 1 |** Relationship between the absolute volume of left hippocampal tail and clinical variables in the Sz group. Relationship between the absolute volume of the left hippocampal tail and **(A)** onset age, **(B)** duration of psychosis, and **(C)** duration of medication in patients with schizophrenia.

observed in schizophrenia patients. Because the exclusion of ARMS individuals with PDD diagnosis did not change the conclusion of the study, the hippocampal findings in ARMS may not be explained only by the coexistence of PDD. However, volumes of these subfields did not differ between schizophrenia and ARMS subjects or between ARMS individuals with and without subsequent transition to psychosis in contrast to a few previous findings (36, 76). As rather small sample size of the ARMS-P individuals ($n = 5$) in our cohort could partly explain such discrepancy, their role as a biological discrimination for subsequent psychosis should be further tested in a larger ARMS-P cohort. Reduced hippocampal subfield volumes commonly observed in schizophrenia and ARMS groups should represent a common biotype involved in vulnerability to psychosis. Recently, approaches that can alter some biotypes, such as deficits in hippocampal perfusion or sensory gating (76–78), have been considered as early interventions for psychosis (79, 80). As aerobic exercise and cognitive enhancement therapy can prevent the hippocampal volume decreases over time in early psychosis (81, 82), this biotype may be one of the target candidates for prophylactic treatment in the future.

In contrast to the conventional notion that hippocampal abnormality is a stable feature of schizophrenia (27–30), the combination of the more marked hippocampal tail atrophy in chronic patients relative to recent-onset patients and its relationship with onset age or duration of psychosis suggests a progressive decrease in the hippocampal subfield volume. Direct group comparison also showed the role of illness stages on the hippocampal tail (ROSz > ARMS > chronic schizophrenia), but this result should be interpreted with cautions due to relatively small sample size of ROSz group and significant group difference in age (although statistically controlled). Although the hippocampal tail has not been well-investigated neuroanatomically (41), previous cross-sectional MRI studies reported that reduced volume of this subfield was observed in schizophrenia patients with a longer duration of psychosis (33, 40) in contrast with those with a shorter duration of psychosis (33, 70). Conversely, two longitudinal studies (33, 39) demonstrated that patients with schizophrenia exhibited progressive volume loss in several hippocampal subfields, such as CA1-4, DG, and subiculum, as opposed to putative ongoing atrophy only in the hippocampal tail in this cohort. These studies

**TABLE 3** | Relationships between the hippocampal volume and clinical variables in the schizophrenia and ARMS groups.

| | ARMS | | | | | | | | | | Sz | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Left hippocampal tail | | Right hippocampal tail | | Right subiculum | | Left CA1 | | Right CA1 | | Right molecular layer HP | | Left hippocampal tail | | Left CA1 | | Right CA1 | | Left molecular layer HP | | Right molecular layer HP | |
| | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* |
| Age at onset (years) | – | – | – | – | – | – | – | – | – | – | – | – | 0.426 | **1.52 × 10$^{-4}$** | −0.020 | 0.866 | −0.081 | 0.491 | 0.040 | 0.734 | 0.019 | 0.872 |
| Duration of psychosis (years) | – | – | – | – | – | – | – | – | – | – | – | – | −0.435 | **1.21 × 10$^{-4}$** | 0.009 | 0.940 | 0.035 | 0.772 | −0.067 | 0.573 | −0.065 | 0.587 |
| Medication dose (HPD equiv., mg/day) | 0.606 | 0.111 | 0.194 | 0.645 | 0.084 | 0.843 | −0.056 | 0.896 | −0.381 | 0.351 | −0.189 | 0.654 | 0.019 | 0.882 | −0.084 | 0.516 | 0.095 | 0.464 | −0.177 | 0.169 | 0.035 | 0.787 |
| Duration of medication (years) | 0.007 | 0.996 | 0.837 | 0.369 | −0.687 | 0.518 | −0.981 | 0.126 | −0.824 | 0.384 | −0.983 | 0.119 | −0.477 | **3.00 × 10$^{-4}$** | −0.028 | 0.843 | −0.054 | 0.702 | −0.093 | 0.509 | −0.122 | 0.384 |
| PANSS positive | −0.002 | 0.987 | 0.051 | 0.734 | 0.101 | 0.499 | −0.018 | 0.906 | 0.175 | 0.240 | 0.034 | 0.821 | −0.243 | 0.040 | −0.104 | 0.383 | −0.036 | 0.766 | −0.062 | 0.605 | −0.129 | 0.281 |
| PANSS negative | 0.249 | 0.091 | 0.193 | 0.195 | 0.268 | 0.069 | 0.320 | 0.028 | 0.286 | 0.052 | 0.288 | 0.049 | −0.007 | 0.956 | 0.015 | 0.897 | 0.123 | 0.304 | 0.084 | 0.482 | 0.100 | 0.405 |
| PANSS general | 0.010 | 0.949 | 0.033 | 0.827 | 0.089 | 0.550 | 0.167 | 0.261 | 0.228 | 0.123 | 0.123 | 0.411 | −0.098 | 0.414 | −0.162 | 0.174 | 0.058 | 0.626 | −0.059 | 0.622 | −0.023 | 0.848 |
| BACS mean z-score | −0.056 | 0.716 | −0.176 | 0.249 | −0.001 | 0.994 | −0.271 | 0.072 | 0.048 | 0.755 | −0.017 | 0.913 | −0.107 | 0.410 | 0.029 | 0.825 | 0.006 | 0.961 | −0.099 | 0.445 | −0.004 | 0.975 |
| SCoRS global rating score | −0.010 | 0.944 | −0.082 | 0.578 | 0.145 | 0.324 | 0.082 | 0.581 | −0.063 | 0.668 | −0.077 | 0.604 | 0.161 | 0.270 | −0.183 | 0.209 | −0.184 | 0.207 | −0.144 | 0.325 | −0.197 | 0.176 |
| SOFAS | 0.002 | 0.990 | −0.086 | 0.601 | 0.035 | 0.831 | −0.317 | 0.049 | −0.115 | 0.485 | −0.047 | 0.777 | −0.135 | 0.387 | 0.136 | 0.385 | −0.059 | 0.708 | 0.084 | 0.591 | −0.061 | 0.700 |

*ARMS, at-risk mental state; BACS, Brief Assessment of Cognition in Schizophrenia; CA, Cornu Ammonis; HP, hippocampus; HPD, haloperidol; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; Sz, schizophrenia.*

*Bold font indicates statistical significance after Bonferroni's correction for multiple comparisons [seven subfields by 10 clinical variables; $p < 0.000714$ (0.05/70)].*

(33, 39) supported the progressive pathology of schizophrenia (19, 25, 26) by confirming that the symptomatic deterioration was synchronized with the decrease in hippocampal volume, although they had limitations; their cohorts were characterized by a relatively small sample size, short-term follow-up period, and mixture of recent-onset and chronic patients. Future large-scale longitudinal studies are required to directly examine the trajectory of the hippocampal subfield atrophy at varying stages of psychotic disorders, focusing on the spatial distribution of subregional deficits.

Although the current MRI study was unable to sufficiently clarify the etiological role of the hippocampus in psychotic disorder, our finding of focal shrinkage in the CA1 and subiculum [molecular layer HP was classified as part of the subiculum or CA fields in most previous segmentations (41, 42)] that developed around onset partly supports the hippocampal hyperactivity models (83, 84). Among them, Small et al. (10) proposed the early involvement of CA1 (and subiculum) in the pathophysiological process responsible for psychosis because it has greater expression of the N-methyl-D-aspartate (NMDA) receptor (85) and may be especially vulnerable to glutamate-mediated neurotoxicity (86). Therefore, excess extracellular glutamate that accumulates preferentially in the CA1/subiculum in the early disease stage affects metabolic demand and blood flow, and causes eventual volume loss in the corresponding region (7, 76, 87). Dysfunction of gamma-aminobutyric acid (GABA)-ergic interneurons, which were proposed to underlie the metabolic and structural alterations in these hippocampal subfields, may propagate to other hippocampal subfields and drive feedforward excitation of the hippocampal trisynaptic circuit (88, 89), leading to the clinical features of schizophrenia and cognitive impairments (90–93). Furthermore, the finding of reduced NMDA receptor related proteins only in the dentate molecular layer in schizophrenia post-mortem brains may imply the specific role of molecular layer in this cascade (94). Alternatively, we previously suggested that only the hippocampal tail exhibits progressive atrophy across the disease stages in contrast to the assumption that hippocampal subfield volume losses extend along the trisynaptic pathway [e.g., CA3-4 and DG; (33)]. In this regard, even though demarcation of the hippocampal tail was slightly different from that in the present study, the cumulative adverse effects of psychotic episodes on the left hippocampal tail have been reported (95). In methylazoxymethanol acetate treated rats as a developmental disruption model of schizophrenia (96), a reduction in synaptic innervation and excitatory synaptic transmission was observed especially in the dorsal hippocampus (97). Thus, the nature of static or progressive structural/functional changes of the hippocampus, particularly in the posterior portion where fewer studies have focused, remains unclear.

Some limitations to the present study should be delineated. First, in order to label the hippocampal subfields, we adopted a new and validated segmentation protocol (41), but it was based on only a T1 sequence, as employed in most previous studies (23, 43, 70). We may be able to obtain more reliable segmentation utilizing an additional T2 sequence (98). Second, hippocampal morphometric changes may be affected not only by intrinsic

factors of psychosis, but also by potential confounding factors such as antipsychotics (99), comorbid anxiety and depression (100), and prolonged stress (101). Future studies should try to replicate the current hippocampal findings in antipsychotic-naïve schizophrenia patients whose comorbid symptoms are well-managed. Thirdly, there are no consensus operational definitions for "resent-onset" or "chronic" schizophrenia [e.g., DSM-IV-TR; (46)]. Although our results did not change significantly between different chronic definitions, potential role of illness stages on the hippocampal volume should be further tested in future longitudinal studies in various illness stages. Fourthly, although the established reliability of automated subfield segmentation (66, 67), our results of significant group difference predominantly in relatively large hippocampal subfields (CA1, molecular layer HP, and hippocampal tail) may raise the possibility of technical issue that prevents accurate group comparison of smaller subfields. Lastly, volume reduction of the hippocampal subfields, especially in the CA1, was also noted in other neuropsychiatric illnesses such as post-traumatic stress disorder, major depressive disorder, and bipolar disorder (102, 103). On the other hand, volume reductions in the CA2/3 and presubiculum were more pronounced in schizophrenia than in bipolar disorder (31), possibly contributing to discrimination among psychiatric disorders. Thus, whether our hippocampal findings belong to a common biotype across psychiatric disorders or a distinct biotype of the schizophrenia spectrum should be investigated.

In conclusion, this MRI study demonstrated that both schizophrenia and ARMS groups exhibit smaller hippocampal volumes, especially in CA1, hippocampal tail, and molecular layer HP subfields. Reduced volume of the left hippocampal tail in schizophrenia was associated with illness chronicity and antipsychotic medication. The hippocampal subfield atrophy may represent a potential biotype that accounts for psychosis vulnerability, but further studies are needed to clarify how it is involved in the formation and development of psychotic disorders.

## DATA AVAILABILITY STATEMENT

The datasets utilized for this article are not available immediately because we do not have permission to share them. Requests to access the datasets should be directed to Daiki Sasabayashi, ds179@med.u-toyama.ac.jp.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee on Medical Ethics of Toyama University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

DS, TT, YT, and MS conceived the present study and its methods. DS conducted statistical analyses and wrote the manuscript. DS, SN, YH, YM, AF, MK, and MN recruited participants, and were involved in clinical and diagnostic assessments. DS and RY analyzed MRI data. KN provided technical support for MRI and data processing. DS, AF, MN, and TT managed MRI and clinical data. TT, YT, and MS contributed to the writing and editing of the manuscript. All authors contributed to and approval the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.642048/full#supplementary-material

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