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Longitudinal changes in striatum and sub-threshold positive symptoms in individuals with an 'at risk mental state' (ARMS)

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ABSTRACT

Recent studies have revealed that several psychotic symptom changes observed in the 'at risk mental state' (ARMS) are associated with changes in the striatum. We investigated if structural changes in the striatum are associated with recovery of sub-threshold psychotic symptoms in subjects with an ARMS who did not develop psychosis (ARMS-N). Sixteen healthy controls and 42 subjects with an ARMS participated in this study. Striatal volumes (caudate, putamen, and nucleus accumbens) were analyzed using MRI. The sub-threshold psychotic symptoms of the subjects with an ARMS were measured using the SOPS. Imaging and symptoms were reevaluated after 52 weeks. Significant right putamen volume reduction was observed at the follow-up in ARMS-N subjects. Improvement in sub-threshold positive symptoms significantly correlated with an increase in volume in the right accumbens at follow up. No relationship was found for negative symptoms. From these findings, the association between improvement in sub-threshold positive symptoms and an increase in the volume of the right accumbens may suggest that changes in the accumbens, which is a major site for dopamine innervation, are associated with symptom recovery. These findings may point to neurobiological resilience that may be associated with lower transition to psychosis.

1. Introduction

The striatum represents the major input structure to the basal ganglia and has been implicated as a crucial site for dopaminergic dysregulation in schizophrenia due to the high density of dopamine receptors. Early work examined the functional integrity of frontal-subcortical circuits (e.g., Pantelis et al., 1992, 1997), while recent work has attempted to more precisely delineate the specific neural circuits that mediate dopamine dysregulation in psychosis. Particular attention has been paid to fronto-striato-thalamic circuits described by Alexander et al. (1986), which topographically link discrete regions of the frontal cortex with specific subregions of the striatum (i.e., caudate, putamen, and nucleus accumbens), pallidum, substantia nigra, and thalamus. The striatum consists of the caudate, putamen, and nucleus accumbens. Each subregion of the striatum is involved in different fronto-striato-thalamic circuits that are responsible for different functions (see Dandash et al., 2017).

However, it remains unclear whether changes in the subregions of the striatum relate to the deterioration of sub-threshold psychotic symptoms, onset of psychosis, or resilience against the transition to psychosis in individuals with an "at-risk mental state (ARMS)" for psychosis. In a positron-emission tomography (PET) study, Howes et al. (2009) reported that ^{18}F-DOPA uptake was elevated in the striatum in subjects with prodromal symptoms of schizophrenia, which were related to the severity of prodromal psychopathology and neuropsychological impairment. Whilst there is evidence for functional changes of fronto-striatal circuits (Dandash et al., 2014), it is unclear whether such relationships may be accompanied by structural changes in the striatum of individuals with an ARMS.

Previous magnetic resonance imaging (MRI) studies on structural changes in the striatum have reported inconsistent results (Breier et al., 1992; Corson et al., 1999; Gunduz et al., 2002; Gur et al., 1998;

Abbreviations: ARMS, at risk mental state; ARMS-P, ARMS subjects who developed psychosis during the 1-year follow-up period; ARMS-N, ARMS subjects who did not develop psychosis during the follow-up period; ARMS-NN, ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the follow-up period; ARMS-NA, ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; SIPS, the Structured Interview for Prodromal Syndrome; SOPS, the Scale of Prodromal Symptoms; POS, the sum of the five SOPS positive items; NEG, the sum of the six SOPS negative items; ΔPOS, one-year change in POS; ΔNEG, one-year change in NEG

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Keshavan et al., 1998; Lang et al., 2001; Oertel-Knöchel et al., 2012; Scherk et al., 2006).

Recent MRI studies on relatively large samples of patients with schizophrenia have reported volume increases in the caudate and putamen, which have been supposedly influenced by the use of typical antipsychotics (Van Haren et al., 2016). Ballmeier et al. (2008) had reported that the un-medicated patients with schizophrenia showed a positive relationship between the severity of affective flattening and local volume reductions in the anterior putamen.

Only a few studies have investigated structural changes in the striatum in people with an ARMS. Among the sub-regions of the striatum, Hannan et al. (2010) investigated whether volumetric abnormalities of the caudate preceded the onset of psychotic illness. In this study, caudate volumes did not differ significantly between individuals with an ARMS and healthy controls and there was no significant difference between converters and non-converters to psychosis.

While around 70% of subjects with an ARMS do not demonstrate positive symptoms that exceed the threshold for psychosis (ARMS-N) (Fusar-Poli et al., 2012), Addington et al. (2011) reported that attenuated positive symptoms may persist in 41% of individuals after 2 years of follow-up. However, few studies have examined the relationship of brain structures with sub-threshold psychotic symptoms and changes over time in these so called “false positive” cases (Cropley et al., 2016; Katagiri et al., 2015). To our knowledge, no study has investigated the longitudinal relationship between sub-threshold psychotic symptom changes and striatal volume changes in subjects with an ARMS.

To elucidate the relationship between changes in sub-threshold psychotic symptoms and the striatal volume in subjects with an ARMS, we investigated the relationship between cross-sectional and longitudinal striatal volume and sub-threshold psychotic symptoms in subjects with an ARMS followed for 1 year. We also investigated the effect of antipsychotics on structural changes in the striatum and recovery from sub-threshold psychotic symptoms.

2. Method

2.1. Participants

The individuals with an ARMS were recruited from the Toho University Omori Medical Center. The participants were diagnosed with an ARMS using the Structured Interview for Prodromal Syndrome (SIPS) (Miller et al., 2003) at the time of the first consultation (baseline). The individuals with an ARMS were treated at the “Youth Clinic” and at the “Il Bosco” day-care center intended for persons with early psychosis (Mizuno et al., 2009). Participants with severe deterioration of clinical symptoms received antipsychotic medication even in the absence of apparent positive symptoms (Yung et al., 2007). The antipsychotics prescribed to subjects were all atypical.

Transition to psychosis during the term of the follow-up period was defined using SIPS. After a 52-week follow-up period, subjects with an ARMS were divided into those who transitioned to psychosis (ARMS-P) and those who did not (ARMS-N). To investigate the influence of antipsychotics on the ARMS-N group, we further divided ARMS-N subjects into those who were not prescribed antipsychotics (ARMS-NN) and those treated with antipsychotics (ARMS-NA). The antipsychotic dosages were expressed as milligram equivalents of chlorpromazine (Woods, 2003) and these values were $\log_{10}$ transformed to reduce skewness (CPZ eq-log). Subjects were excluded if they had a history of alcohol dependence, substance abuse, or a neurological illness. Healthy control subjects were recruited among students of a neighboring university, their relatives, acquaintances, and also from independent sources in the community. Written informed consent was obtained from all participants after the study had been explained in full. This study was approved by the Ethics Committee of Toho University.

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

The Scale of Prodromal Symptoms (SOPS) is a 19-item scale designed to measure the severity of prodromal symptoms and changes over time included in the SIPS (Miller et al., 1999).

The SOPS includes subscales for Positive and Negative symptoms. We calculated the state of the sub-threshold symptoms of the subjects with an ARMS by separately summing five positive SOPS items (POS score) and six negative SOPS items (NEG score) at both baseline and at 52 weeks. To use these values in the longitudinal analysis, the 1-year changes in the POS and NEG scores were calculated by subtracting the relevant baseline score from the score at 52 weeks (i.e., ΔPOS and ΔNEG).

2.3. Image acquisition

The subjects with an ARMS and the controls underwent brain MRI (EXCELART Vantage, XGV 1.5 T; Toshiba Medical Systems, Tokyo, Japan) at baseline, and three-dimensional T1-weighted images were acquired. Imaging parameters were: repetition time, 24.4 ms; echo time, 5.5 ms; 2-mm-thick; matrix, 256 × 256; field of view, 250 × 250 mm; FA, 35; sagittal. We rescanned the ARMS group using the same MRI scanner at 52 weeks after baseline.

2.4. Image processing

The structural scans were processed using FreeSurfer V 5.2 (https://surfer.nmr.mgh.harvard.edu). The T1-weighted MR images were preprocessed in accordance with a standard automatic reconstruction algorithm (Fischl, 2012). Freesurfer produces volume estimates of structures (in mm^3) (Fig 1). All reconstructed images were carefully inspected. One MRI dataset for an ARMS-NA subject with severe artifacts in the baseline scan was excluded.

To investigate the longitudinal volume changes in the subregions of the striatum, we examined the volumes of the bilateral caudate, putamen, and accumbens; the intracranial volume (ICV) was also ascertained; volumes were derived from the asegstats2table program (https://surfer.nmr.mgh.harvard.edu/fswiki/asegstats2table).

The 1-year volume changes for each of the striatal subregions (Δ subregion of the striatum) were calculated by subtracting each volume of the striatal subregion at baseline from the volume at 52 weeks (i.e., Δ left caudate, Δ left putamen, Δ left accumbens, Δ right caudate, Δ right putamen and Δ right accumbens).

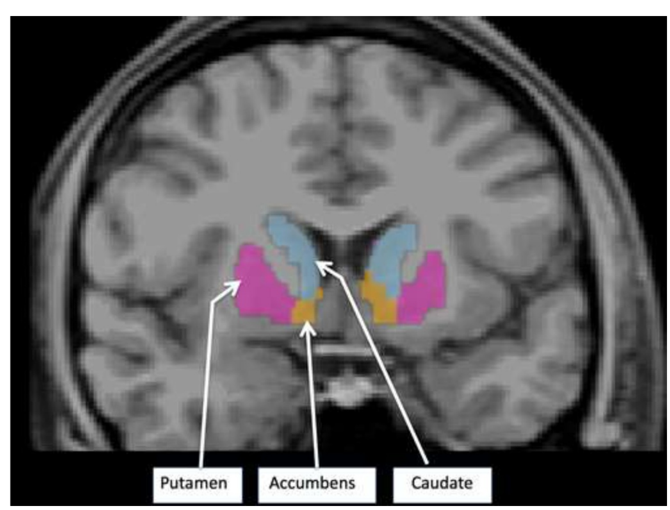

Fig. 1. Schema of segmentation of subregions within the striatum using Freesurfer.

2.5. Statistical analysis

Data were analyzed using SPSS version 20 (www.spss.com). A *p*-value of <0.05 was regarded as significant.

2.5.1. Cross sectional differences in POS and NEG scores and volume of the subregions of the striatum among groups

Analysis of variance (ANOVA) was used to compare the age and the volumes of the striatal subregions among the control, ARMS-NN, ARMS-NA, and ARMS-P groups and to compare the POS and NEG scores among the ARMS-NN, ARMS-NA, and ARMS-P groups at baseline. Tukey's test was used for post-hoc analyses.

2.5.2. Longitudinal volume changes in the POS and NEG scores and striatal subregions in ARMS-N subgroups

We examined the longitudinal changes in the POS and NEG scores and all striatal subregional volumes, comparing those in the ARMS-NN group with those in the ARMS-NA group, using a repeated measures ANOVA that included a between-group factor (ARMS-N subgroups) and a within-subject factor (baseline and 52 weeks).

2.5.3. Relationship between the POS and NEG scores and volume changes in the striatal subregions in the ARMS-N group

We used multiple regression analysis to investigate the longitudinal relationship between changes in striatal subregional volumes and changes in POS and NEG scores during the follow-up period in the ARMS-N groups and to assess the contribution of other factors. The mean antipsychotic dosage during the 1-year follow-up period was calculated as the mean value of the antipsychotic dosage (milligram equivalents of chlorpromazine) at two time points (baseline and 52 weeks), and the mean dosage for each person was $\log_{10}$ transformed to reduce skewness (CPZeq-mean-log). ΔPOS and ΔNEG were used as dependent variables, and age, sex, between-scan intervals, CPZ eq-mean-log, ICV, and left and right Δ caudate, Δ putamen, and Δ accumbens, were used as independent variables. The variables were excluded using a stepwise selection. The variance inflation factor (VIF) was employed to check for multicollinearity.

3. Results

3.1. Cross sectional analysis at baseline

The demographic and clinical characteristics of the groups undergoing clinical assessments and MRI are shown in Table 1. Participants were sixteen controls (eight male and eight female) and 42 subjects with an ARMS (12 male and 30 female). Five (one male and four female) of the 42 (11.9%) subjects with an ARMS transitioned to psychosis during the 1-year follow-up period (ARMS-P). Of those 37 ARMS-N subjects, 23 (six male and 17 female) were prescribed antipsychotics (ARMS-NA) during the follow-up period.

The control, ARMS-NN, ARMS-NA, and ARMS-P groups did not differ in sex (χ^2 (3) = 2.896, $p = 0.408$) or age (ANOVA, F (3,54) = 1.853, $p = 0.152$) at baseline.

All ARMS-P subjects and 20 of the ARMS-NA subjects had been prescribed antipsychotics at baseline. No difference in baseline antipsychotic dosage was found between the ARMS-NA and ARMS-P groups ($t = -0.378$, $p = 0.709$). At baseline, there were no significant differences in POS (ANOVA, F (2,34) = 0.833, $p = 0.443$) and NEG (ANOVA, F (2,32) = 1.425, $p = 0.255$) scores among the ARMS-NN, ARMS-NA, and ARMS-P groups. There were no significant differences in striatal sub-regional volumes among the control, ARMS-NN, ARMS-NA, and ARMS-P groups at baseline.

In this study, we did not follow up with the healthy controls, while among the ARMS-P subjects, only three underwent both MRI and POS and NEG assessment at both baseline and at 52 weeks, thus, the main results concern only the ARMS-N groups.

3.2. Longitudinal analysis

3.2.1. Changes in POS and NEG scores in the ARMS-N subgroups

Repeated measures analysis examining POS changes over time indicated that there was no significant main effect of group (F (1,24) = 0.751, $p = 0.395$) and no significant time × group interaction (F (1,24) = 3.428, $p = 0.076$) between ARMS-NN and ARMS-NA groups. However, there was a significant effect of time for POS score (F (1,24) = 20.287, $p < 0.001$).

In the comparison of NEG scores, the effects of time (F (1,17) = 2.537, $p = 0.130$), time × group interaction (F (1,17) = 0.685, $p = 0.419$), and group (F (1,17) = 3.421, $p = 0.082$) were not significant.

3.2.2. Changes in volume of the subregions of the striatum in the ARMS-N subgroups

The total left and right putamen volumes showed a significant effect of time between the ARMS-NN and ARMS-NA groups (F (1,32) = 7.957, $p = 0.008$) but no significant effect of group or time × group interaction (Tables 1 and 2). To investigate the difference in the course of reduction in the left and right putamen volumes, we further analyzed the longitudinal changes in the left and right putamen volumes respectively. The right putamen volume showed a significant effect of time between the ARMS-NN and ARMS-NA groups (F (1,32) = 5.476, $p = 0.026$) but no significant effect of group (F (1,32) = 0.598, $p = 0.445$) or time × group interaction (F (1,32) = 2.095, $p = 0.157$). There were no significant effects detected in the other striatal subregions.

3.2.3. Regressors of longitudinal changes in psychiatric symptoms (POS and NEG) in the ARMS-N group

For the stepwise regression analysis for ΔPOS in the ARMS-N groups, the model for ΔPOS was significant (F (2,22) = 12.548, $p < 0.001$, $R^2 = 0.533$, adjusted $R^2 = 0.490$) and identified the right accumbens ($\beta = -0.64$, $p < 0.001$) and CPZ eq-mean-log ($\beta = -0.34$, $p = 0.029$) as significant predictors. The VIF was 1.00, which signifies that there was no collinearity in the model (Table 3).

4. Discussion

In this study, we investigated the relationship between changes in striatal subregional volumes and changes in sub-threshold psychotic symptoms in pre-psychotic individuals considered ‘at-risk for psychosis.’ There were no baseline volumetric differences among controls, the ARMS-N subgroups, and ARMS-P subjects. Our findings are consistent with those of previous studies that reported no subcortical, including striatal, volume differences between healthy controls and subjects at high risk for psychosis (Hannan et al., 2010; Harrisberger et al., 2016).

Our longitudinal assessment of the ARMS-N groups identified significant volume reduction in the right putamen. While numerous volumetric brain changes have been linked to exacerbation of positive symptoms in schizophrenia, there have been variable reports of specific volume changes in the putamen. Perhaps most consistently reported are increases in putamen volume, being most prominent in the chronic phase of the illness (van Erp et al., 2016) and associated with typical antipsychotic medication use (Rimol et al., 2010; Scherk et al., 2006; Van Haren et al., 2016).

Jorgensen et al. (2016) reported that first-generation antipsychotic users had larger bilateral putamen and right caudate volumes compared to healthy controls and that right putamen volumes were significantly larger in these subjects compared to second-generation antipsychotic users. Although some of our ARMS-N subjects had been prescribed antipsychotics during the year of follow up (ARMS-NA), the dosage of antipsychotics was low and the antipsychotics prescribed to all subjects were atypical. Thus, the significant reduction in putamen volume in our

Table 1
Demographic data, scores for sub-threshold positive symptoms (POS) and negative symptoms (NEG), and the volume of the of the striatal subregions.

	Baseline Control	ARMS-NN	ARMS-NA	ARMS-P	p	52 week ARMS-NN	ARMS-NA	ARMS-P	p
Participants (male/female)	n = 16 (8/8)	n = 14 (5/9)	n = 23 (6/17)	n = 5 (1/4)	0.408	n = 14 (5/9)	n = 23 (6/17)	n = 5 (1/4)	0.741
Age (year)	23.19 (2.857)	25.43 (7.743)	23.35 (6.485)	18.20 (4.207)	0.152	26.36 (7.69)	24.48 (6.45)	19.00 (4.47)	0.124
Subjects who underwent the POS assessment (male/female)		n = 11 (3/8)	n = 21 (4/17)	n = 5 (1/4)	0.862	n = 8 (2/6)	n = 18 (4/14)	n = 3 (1/2)	0.915
POS score		17.36 (3.264)	19.05 (4.177)	19.80 (5.450)	0.443	14.13 (4.155)	13.22 (4.953)	17.00 (5.196)	0.45
Subjects who underwent the NEG assessment (male/female)		n = 10 (3/7)	n = 20 (4/16)	n = 5 (1/4)	0.817	n = 5 (0/5)	n = 15 (3/12)	n = 3 (1/2)	0.437
NEG score		21.8 (3.084)	18.65 (4.534)	18.2 (9.68)	0.255	19.6 (3.209)	14.27 (6.239)	13.0 (3.00)	0.154
Subject underwent MRI (Male/female)	n = 16 (8/8)	n = 14 (5/9)	n = 22 (6/16)	n = 5 (1/4)	0.448	n = 13 (5/8)	n = 22 (5/17)	n = 4 (1/3)	0.6
Between-scan intervals (weeks)						59.23 (10.35)	52.09 (12.47)	50.25 (11.50)	0.183
Volume of left caudate	3447 (437)	3508 (434)	3711 (498)	3660 (239)	0.298	3542 (498)	3643 (493)	3432 (303)	0.666
Volume of left putamen	5711 (733)	5500 (1063)	5476 (742)	5601 (532)	0.833	5420 (1048)	5292 (576)	5565 (260)	0.756
Volume of left accumbens	606 (71)	589 (144)	583 (113)	602 (94)	0.934	579 (116)	575 (95)	604 (61)	0.866
Volume of right caudate	3773 (357)	3841 (477)	3801 (569)	3868 (337)	0.972	3769 (500)	3769 (527)	3812 (372)	0.987
Volume of right putamen	5614 (545)	5524 (978)	5301 (793)	5542 (405)	0.623	5251 (787)	5145 (706)	5343 (368)	0.838
Volume of right accumbens	544 (83)	471 (113)	501 (91)	530 (33)	0.174	477 (126)	510 (73)	526 (71)	0.511
Volume of ICV	1,313,548 (173,420)	1,299,748 (252,334)	1,304,935 (210,927)	1,297,845 (139,219)	0.998	1,293,706 (268,704)	1,282,444 (194,328)	1,239,771 (92,988)	0.909
Subject underwent MRI and SOPS at baseline and 52 week (Male/female)		n = 8 (2/6)	n = 17 (4/13)	n = 3 (1/2)	0.937	n = 8 (2/6)	n = 17 (4/13)	n = 3 (1/2)	0.937
Who prescribed antipsychotics			n = 20 (5/15)	n = 5 (1/4)	0.815		n = 21 (5/16)	n = 5 (1/4)	0.856
Dose of CPZ eq			98.60 (58.31)	127.00 (109.31)	0.425		111.52 (72.14)	178.80 (147.38)	0.143
Dose of CPZ eq-log			1.920 (0.267)	1.975 (0.389)	0.709		1.966 (0.275)	2.095 (0.459)	0.415

ARMS-NN: ARMS subjects who did not develop psychosis and were not prescribed antipsychotics during the 1-year follow-up period; ARMS-NA: ARMS subjects who did not develop psychosis but were prescribed antipsychotics during the follow-up period; ARMS-P: ARMS subjects who developed psychosis during the follow-up period; POS: sub-threshold positive symptoms; NEG: negative symptoms; CPZ eq-log: $\log_{10}$ transformed antipsychotic dosage milligram equivalents of chlorpromazine.

ARMS-N subjects is consistent with similar findings in drug-naive patients with schizophrenia. Our results indicated that ARMS-N subjects show some progressive biological alteration in the right putamen. The putamen plays a role in some types of learning such reinforcement and implicit and category learning (Ell et al., 2006; Packard and Knowlton, 2002). Additionally, in schizophrenia, Ballmaier et al. (2008) reported a significant positive correlation between right anterior putamen surface contractions and affective flattening, a core negative symptom, suggesting that such change was related to greater illness severity. However, in the present study with individuals at high-risk for psychosis, changes in putamen volume did not correlate to the changes in positive as well as negative symptoms.

In contrast, we observed that longitudinal recovery of sub-threshold positive symptoms in ARMS-N subjects was related to increased right accumbens volume over the follow-up period. In our regression analysis, changes in the right accumbens over the 1-year follow-up period and mean dosage of antipsychotics were significant predictors of positive symptom change. These results indicate that improvement in sub-threshold symptoms (i.e., reduced symptoms) were associated with an increase in the volume of the accumbens (as well as with medication), suggesting that the accumbens and putamen may be acting in differential manners on the features of psychosis.

The nucleus accumbens is the most inferior part of the striatum. The prefrontal cortex regulates the activity of the nucleus accumbens through direct excitatory inputs to GABA projecting neurons and indirectly through its action on dopamine and acetylcholine inputs (Montaron et al., 1996; Sesack and Pickel, 1992). The role of the nucleus accumbens in motor behavior, motivation, and reward has been repeatedly reported (Berridge and Robinson, 1998; Hoebel et al., 2007) (see Del Arco and Mora, 2009). In schizophrenia, dysfunction of the nucleus accumbens has been linked to attention and cognitive deficits (Dempster et al., 2017), dysfunction of reward processing (Grace, 2000; Juckel et al., 2006), aberrant salience processing (Berridge and Robinson, 1998; Morrison and Murray, 2009), motivational deficits and negative symptoms (Waltz and Gold, 2016), and thought disorder (Ballmaier et al., 2004) and has been identified as a key therapeutic target of interest in schizophrenia (Mikell et al., 2009). Despite the above evidence, the results of previous reports on the structure and volume change of the nucleus accumbens in patients with schizophrenia have been inconsistent (Ballmaier et al., 2008; Forns-Nadal et al., 2017; Gunduz et al., 2002; Van Haren et al., 2016). There have been few reports on longitudinal volume change in the nucleus accumbens in subjects with an ARMS subjects. In our study, while the volume of the bilateral accumbens did not differ between the control

Table 2
Differences in longitudinal changes (between baseline and 52 weeks) in the volumes of striatal subregions between the ARMS-NN and ARMS-NA groups.

	Effect of time			Time × group interaction		Main group effect	
	F (1,32)	p		F (1,32)	p	F (1,32)	p
Total volume of left and right caudate	0.218	0.644		1.124	0.297	0.094	0.761
Total volume of left and right volume of putamen	7.957	0.008	**	1.085	0.305	0.422	0.521
Total volume of left and rightl volume of accumbens	0.046	0.832		1.036	0.316	0.023	0.881

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

Table 3
Results of the stepwise regression analysis for ΔPOS in the ARMS-N group.

Dependent variables	Indipendent vriables	Standradized Coefficients β	t	p	(95% CI)			VIF	
Δ POS	Δ right accumbens	−0.64	−4.393	0.000	−0.085	to	−0.031	1.000	**
	CPZeq-mean-log	−0.34	−2.333	0.029	−3.733	to	−0.219	1.000	*

F (2,22) = 12.548, $p < 0.001$, $R^2 = 0.533$, adjusted $R^2 = 0.490$.
(ARMS-N: ARMS subjects who did not develop psychosis during the 1-year follow-up period; Δ right accumbens: one-year change in right accumbens volume; CPZeq-mean-log: $\log_{10}$ transformed milligram equivalents of chlorpromazine; POS: sub-threshold positive symptoms; ΔPOS: one-year change in sub-threshold positive symptoms) *$p < 0.05$. **$p < 0.01$.

and ARMS subgroups at baseline, and there was no significant longitudinal volume increase, the relationship between increased volume of the right accumbens with significant improvement of sub-threshold symptoms suggests that this region may be relevant to positive symptom recovery.

The putamen and accumbens are part of the dorsal and ventral striatum, respectively. Thus, the putamen and accumbens are represented in different fronto-striato-thalamic circuits that are responsible for different functions (Draganski et al., 2008; Haber, 2003) and there is evidence suggesting that they are differentially affected in relation to psychosis transition (see Dandash et al., 2017).

Our findings of longitudinal volume reduction of the putamen raise the possibility that this reduction relates to the progressive neurobiological risk for developing psychosis as a “risk” factor. However, the finding of volume increase in the right accumbens over the 12-month period was associated with recovery of subthreshold psychotic symptoms, which may relate to “protective” factors or “neurobiological resilience” (Pantelis and Bartholomeusz, 2014).

There are several limitations to this study. The power is limited particularly by the small number of controls, and more so by the subdivision of subjects with an ARMS into subgroups based on transition status and medication status. Further, there was no longitudinal control group. Thus, we could not exclude a possible normal aging effect on the volume changes in the striatum (Van Haren et al., 2016). In this study, five of the 42 (11.9%) subjects with an ARMS transitioned to psychosis during the 1-year follow-up period (ARMS-P). However, a substantial proportion of people at clinical high risk of psychosis will develop a psychotic disorder over time. Fusar-Poli et al. (2012) reported that the transition risk was 22% after 1 year and 36% after 3 years. Thus, there is a possibility that some ARMS-N subjects transitioned to psychosis after the study period. Thus, our study should be replicated using a larger sample of subject with an ARMS and controls.

In addition, the sample was composed primarily of female, which may have influenced the results. Moreover, it is possible that the individuals who were able to complete all scanning and neuropsychological testing protocols may differ in various respects from individuals that were not able to comply with this level of follow-up.

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Conflict of interest

All authors declare no conflicts of interest.

Supplementary materials

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