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Hippocampal volume reduction in chromosome 22q11.2 deletion syndrome (22q11.2DS): A longitudinal study of morphometry and symptomatology

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ABSTRACT

Recent studies observed an association between the structural integrity of the hippocampal structure and the manifestations of clinically significant psychotic symptoms in participants at high risk for psychosis. The present study sought to investigate the longitudinal trajectory of the hippocampal volume and its subregions among a sample of participants affected by 22q11.2 deletion syndrome (22q11.2DS), a neurogenetic disorder associated with elevated risk for psychosis. We specifically investigated possible correlations between hippocampal volumes, as measured by magnetic resonance imaging (MRI), and the manifestation of positive psychotic symptoms (hallucinations and delusions). Regional hippocampal volumes were measured twice with cerebral MRI obtained at 3-year intervals in 30 healthy participants and 31 gender-matched 22q11.2 microdeletion carriers aged 6 to 22. We examined potential associations between psychotic symptom manifestations and volumetric parameters at both time points. We found a hippocampal body-driven significant reduction in hippocampal volume among patients with 22q11DS compared to controls. No significant group by time interaction for the total or the subregional volumes were observed. In patients, larger hippocampal head at baseline was associated with the presence of hallucinations at follow-up. We first discuss the reduced hippocampal body finding in light of potentially abnormal mesocortical circuits. We further discuss the association between baseline hippocampal head volume in participants with 22q11DS as a possible marker related to the later unfolding of psychotic symptoms.

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1. Introduction

22q11.2 deletion syndrome (22q11DS), also known as velocardiofacial syndrome (VCFS), is caused by a 3-Mb deletion on chromosome 22 of more than 40 genes including the catechol-O-methyltransferase (COMT) polymorphism, a well-studied gene in schizophrenia research (Gothelf et al., 2005; Harrison and Weinberger, 2005). The 22q11.2 deletion syndrome affects between 1:2000 (Robin and Shprintzen, 2005) and 1:6000 individuals, depending on the employed clinical criteria (Botto et al., 2003). This neurodevelopmental condition encompasses a wide spectrum of somatic, cognitive and psychiatric disorders, including a schizophrenic-like phenotype (Lewandowski et al., 2007) that led investigators to consider the syndrome as a model for studying the onset of schizophrenia.

The consistent reporting of hippocampal volume reduction in schizophrenic patients as compared to controls suggests that this structure plays an essential role in the pathogenesis of schizophrenia (Narr et al., 2004; Vita et al., 2006; Zhou et al., 2008; Witthaus et al., 2010). As a result, the study of hippocampal structure in 22q11DS has evoked

increased interest. To date investigations based on cross-sectional samples reported a total hippocampal volume reduction in the syndrome (Debbané et al., 2006; Kates et al., 2006; Deboer et al., 2007), which persisted after correction for brain volume in most studies (Debbané et al., 2006; Deboer et al., 2007). However longitudinal studies are now required to determine whether the hippocampal reduction is a state feature of 22q11DS deletion syndrome, reflecting the susceptibility to psychosis, or a trait feature associated with the onset of schizophrenia within the affected participants. The only longitudinal study to date that assessed hippocampal development in 22q11DS comprised 19 affected participants and 18 controls (Gothelf et al., 2007). The authors did not report any significant difference of hippocampal volume between the 22q11DS participants and the healthy controls at baseline. Further investigations demonstrated no significant time by group (controls, 22q11DS participants with and without psychosis) interaction on whole hippocampal volume in the 4.9-year interval (interval range between 3.5 and 6.4 years).

Most neuroimaging studies published to date report measurements of total hippocampal volume without taking into account its regional specificity. However, the hippocampus maturation is characterized by heterogeneous trajectories of volumetric changes with differential growth and reduction over years of the hippocampal subregions in both normal controls (Gogtay et al., 2006) and patients with childhood onset schizophrenia (Nugent et al., 2007). The

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heterogeneous trajectories of the hippocampal subvolumes might be explained by differences in cerebral inputs and outputs connecting each region. In turn, the rostrocaudal heterogeneity may subserve the functional specificity of the hippocampal substructures. In relation to psychosis, we further note that the anterior portion of the hippocampus appears to be specifically associated with the emergence of psychotic symptoms (Lodge and Grace, 2008).

In the present study, we aim at assessing the developmental trajectory of the hippocampal segments in youngsters with 22q11 deletion syndrome. We also seek to investigate potential relationships between hippocampal morphology and clinical features shared by 22q11DS and schizophrenic patients: altered memory skills (Lewandowski et al., 2007; Debbané et al., 2008) and positive psychotic symptoms (i.e. hallucination and/or delusions). In order to achieve these goals, we examined data from 30 patients with 22q11DS aged 6 to 21 years and 31 controls aged 7 to 22 years. All individuals underwent neuroimaging and psychiatric screening at two timepoints within a time interval of 3.1 years. For a precise extraction of the hippocampal volume and of its subregions, we chose the use of manual tracing, considered as a highly reliable method for measuring temporomesial structures (Tae et al., 2008). Following previous reports on participants at high risk for psychosis, with the constant follow-up interval (3.1 ± 0.2 years) of our sample, we expect to find disturbed hippocampal maturation in our 22q11DS group. Further, consistent with recent memory skill investigations in this population, we also expect reduced memory performances in the 22q11DS group. Finally, on the basis of research examining the hippocampal structure in youths at high risk for psychosis, we expect that structural differences in the anterior portion of the hippocampus may constitute a potential predictor for psychotic manifestations in our large 22q11DS sample.

2. Methods

2.1. Participants

We included all the patients who were part of our project cohort since 2001 and who were aged 6 to 22 years at the first timepoint (T1) and whose follow-up time interval (between baseline and the second timepoint, T2) ranged between 2.7 and 4 years. The inclusion criteria for the project's cohort are as follows: participants with confirmed 22q11.2 deletion, participants who were at least 6 years of age at baseline, and participants who had English or French as their first language. Among the controls, we excluded all participants with past or present neuropsychiatric disease, or with any somatic disease that may have interfered with neurodevelopment (including major operations, head injury with loss of consciousness, cardiac manifestations, diabetes).

2.1.1. Individuals with 22q11DS

Thirty-one patients (12 males and 19 females) aged 6 to 21 years (mean 11.4 ± 4.09) were recruited through local patients associations. A written informed consent was received from all participants and/or parents according to protocols approved by the Institutional Review Board of Geneva University School of Medicine. The 22q11.2 deletion was confirmed in all patients by PCR direct sequencing. In the 22q11DS group, the distribution of the COMT polymorphism was as follows: 14 carriers of the Met allele (8 F/6 M, aged 12.4 ± 6.65 years) and 17 carriers of the Val allele (11 F/6 M, aged 10 ± 3.5 years).

The group had a mean full scale IQ score of 70.2 ± 11.5 at the first visit (baseline T1) and 70.7 ± 13.6 at the second visit (follow-up T2) as measured by the Wechsler Intelligence Scale for Children (Wechsler, 1991) or the Wechsler Adult Intelligence Scale for adults (Wechsler, 1997a). The participants' specific memory scores assessed with the Children's Memory Scale (Cohen, 1997) and the Wechsler Memory Scale (Wechsler, 1997b) at baseline were as follows: verbal immediate 86 ± 14 , delay 84 ± 18 and visual immediate 76 ± 16 , delay 79 ± 15 .

The presence of psychotic symptoms (hallucinations or delusions) was determined by an experienced child and adolescent psychiatrist (S.E.), using semi-structured interviews with patients and their parents: the Diagnostic Interview for Children and Adolescents (Reich, 2000) and the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1992). Among the participants, eight presented psychotic symptoms at T1: four had delusions and hallucinations, two had delusions only, and two had hallucinations only. Seventeen presented psychotic symptoms at T2: eight had delusions and hallucinations, three delusions only and six hallucinations only. Seven patients were under psychotropic medication at T1 and/or T2.

2.1.2. Comparison group

Thirty healthy typically developing individuals (12 males and 18 females) aged 7 to 22 years (mean 12.5 ± 5.06) were recruited within local schools and community. The absence of neurological or psychiatric disorder was assessed during a medical interview by

S.E. using standardized scores: Child Behaviour Checklist for minors (Achenbach and Ruffle, 2000), and Symptom Checklist 90 (Derogatis et al., 1976) for individuals older than 18.

The control group had a mean full scale IQ score at T1 of 112 ± 12.8 , and 109 ± 11.6 at T2. Their specific memory scores at baseline were 113 ± 17 for verbal immediate, 111 ± 17 for verbal delay and 108 ± 17 for visual immediate, 104 ± 15 for visual delay.

2.2. Image processing and hippocampus tracing

Cerebral magnetic resonance images were acquired using a Philips Intera 1.5 T scanner. Details on sequence parameters and pre-processing have been previously described (Dufour et al., 2008). Delineation of the amygdala, to identify the most anterior hippocampal part, and the hippocampus was performed rostrocaudally on coronal slices according to a previously published protocol (Kates et al., 1997). SPGR datasets were transformed from a 256×256 to a 512×512 resolution using bicubic interpolation to allow more precision in the ROI (region of interest) demarcation. Delineation of the hippocampus was performed on coronal slices realigned according to the AC-PC (anterior commissure–posterior commissure) plane. Segmentation into head, body and tail was performed according to our previous publication (Debbané et al., 2006).

For all procedures two independent raters, blind to the participants' diagnoses, randomly chose 10 participants' MR images on which they delineated the amygdala and the hippocampus. The inter-rater alpha correlation coefficients were 0.96 and 0.91 respectively.

2.3. Statistical analyses

An alpha of 0.05 (two-tailed) was used as a threshold for statistical significance in all analysis.

Analyses of variance (ANOVAs) were used to assess the effect of diagnosis on cerebral grey matter and total left and right hippocampal volumes. We performed multivariate analyses of covariance (MANCOVAs) to identify relevant variations in hippocampal subregional volumes between 22q11DS participants and controls while adjusting for the effect of cerebral grey matter volume differences between the two groups. The significant volumetric parameters were then covaried for age, gender, and full scale IQ. Before performing repeated measures ANOVA, we first compared longitudinal volumetric variations of the hippocampal subregions between the two groups; next we assessed the association of hippocampal volumes at T1 with the existence of psychotic symptoms at T2 among participants with 22q11DS.

3. Results

As reported in Table 1, significant bilateral reductions in cerebral and hippocampal volumes were observed in the group of patients compared to controls. In both groups a rightward asymmetry, stronger in the anterior part, was evidenced ($p < 0.001$; 22q11DS $F(1,30) = 42.1$, controls $F(1,29) = 27.9$). The asymmetry was not significantly different between the two groups ($p = 0.628$). Further MANCOVAs showed significant reduction of all hippocampal subregions in the 22q11DS group compared to controls, with the most significant volumetric difference being found in the hippocampal body ($p = 0.0001$, $F = 15.0$; see Table 1). With covariation for age, full scale IQ and gender, the body reduction remained strikingly significant ($p = 0.001$), while the head and tail reduction withstood covariation for age and gender only.

As shown in Fig. 1, no group-specific longitudinal changes were observed in the total hippocampal volumes ($p = 0.719$) nor in the subregions (all $p > 0.114$). We did not find any significant relation between hippocampal subregional volumes and specific memory skills in the control nor in the 22q11DS group and there was no significant link between hippocampal volumes and COMT polymorphism among the microdeletion carriers. As illustrated in Fig. 2, the presence of hallucinations at T2 was greater among 22q11DS participants who had larger hippocampal head volumes at T1 (Wilks lambda 0.518; $p = 0.012$, $F(1,29) = 7.22$). Results remained significant after covarying for age ($p = 0.032$), or for COMT polymorphism ($p = 0.036$), as well as after the exclusion of the seven patients exposed to psychotropic medication at any timepoint ($p = 0.04$). No correlation was observed with delusions.

4. Discussion

Our study is the first to date to assess the longitudinal volumetric trajectory of hippocampal subregions in 22q11DS. Applying one of

Table 1

Cerebral and hippocampal volume comparisons for 22q11DS vs control subjects at T1, T2 and longitudinal change (T2–T1); volume expressed in cm³. (For a better visualization refer to Fig. 1).

T1	22q11DS	Controls	F	p	p (covaried for age and gender)
Cerebrum					
Tissue	997.3 ± 137.5	1090.1 ± 92.6	9.63	0.003	0.001
Grey	618.1 ± 61.7	659.7 ± 70.7	6.00	0.017	0.002
White	379.2 ± 82	431.1 ± 60.0	7.88	0.007	0.002
Hippocampus					
Bilateral	3.07 ± 0.45	3.57 ± 0.39	21.72	0.0001	0.0001
Left	1.46 ± 0.23	1.72 ± 0.16	25.33	0.0001	0.0001
Right	1.62 ± 0.23	1.87 ± 0.25	15.39	0.0001	0.0001
Bilateral head	1.65 ± 0.29	1.85 ± 0.33	6.72	0.012	0.014
Head left	0.75 ± 0.14	0.86 ± 0.17	7.54	0.008	0.010
Head right	0.90 ± 0.18	1.00 ± 0.19	4.57	0.037	0.044
Bilateral body	1.09 ± 0.21	1.31 ± 0.22	15.02	0.0001	0.0001
Body left	0.54 ± 0.12	0.65 ± 0.11	13.48	0.001	0.001
Body right	0.55 ± 0.11	0.66 ± 0.11	13.88	0.0001	0.0001
Bilateral tail	0.33 ± 0.11	0.41 ± 0.07	10.53	0.002	0.003
Tail left	0.16 ± 0.07	0.21 ± 0.05	8.52	0.005	0.007
Tail right	0.17 ± 0.06	0.20 ± 0.04	7.17	0.010	0.013
T2	22q11DS	Controls	F	p	p (covaried for age and gender)
Cerebrum					
Tissue	1006.9 ± 119.1	1095.8 ± 98.2	10.10	0.002	0.0001
Grey	602.0 ± 62.6	655.8 ± 73.0	9.600	0.003	0.0001
White	404.9 ± 75.7	440.0 ± 52.6	4.382	0.041	0.030
Hippocampus					
Bilateral	3.16 ± 0.43	3.68 ± 0.44	22.22	0.0001	0.0001
Left	1.50 ± 0.23	1.74 ± 0.21	17.74	0.0001	0.0001
Right	1.65 ± 0.23	1.94 ± 0.25	21.77	0.0001	0.0001
Bilateral head	1.69 ± 0.32	1.90 ± 0.35	5.885	0.018	0.018
Head left	0.77 ± 0.18	0.88 ± 0.20	4.57	0.037	0.036
Head right	0.91 ± 0.18	1.02 ± 0.18	5.14	0.027	0.028
Bilateral body	1.11 ± 0.19	1.35 ± 0.21	23.09	0.0001	0.0001
Body left	0.55 ± 0.10	0.65 ± 0.12	12.57	0.001	0.001
Body right	0.56 ± 0.11	0.70 ± 0.11	28.50	0.0001	0.0001
Bilateral tail	0.36 ± 0.12	0.43 ± 0.11	4.95	0.030	0.029
Tail left	0.18 ± 0.08	0.21 ± 0.07	2.50	0.119	0.112
Tail right	0.18 ± 0.06	0.22 ± 0.05	6.82	0.011	0.011
T2–T1	22q11DS	Controls	F	p	
Cerebrum					
Tissue	9.51 ± 38.25	5.00 ± 25.32	0.29	0.590	
Grey	–1.61 ± 32.43	–3.88 ± 29.61	2.39	0.127	
White	2.57 ± 14	8.88 ± 35.01	4.67	0.035	
Hippocampus					
Bilateral	0.08 ± 0.27	0.10 ± 0.25	0.13	0.719	
Left	0.05 ± 0.14	0.02 ± 0.14	0.35	0.558	
Right	0.04 ± 0.15	0.08 ± 0.13	1.60	0.211	
Bilateral head	0.04 ± 0.17	0.04 ± 0.14	0.01	0.943	
Head left	0.02 ± 0.11	0.02 ± 0.11	0.00	0.951	
Head right	0.01 ± 0.10	0.02 ± 0.07	0.04	0.838	
Bilateral body	0.01 ± 0.17	0.05 ± 0.17	0.62	0.433	
Body left	0.01 ± 0.10	0.00 ± 0.10	0.07	0.799	
Body right	0.01 ± 0.10	0.05 ± 0.10	2.58	0.114	
Bilateral tail	0.03 ± 0.06	0.02 ± 0.08	0.46	0.501	
Tail left	0.02 ± 0.04	0.00 ± 0.06	1.00	0.321	
Tail right	0.01 ± 0.04	0.01 ± 0.04	0.02	0.961	

the most accurate existing methods to delineate the hippocampus in a strictly selected longitudinal sample, we observed the following: a) a bilateral reduction of the hippocampus in 22q11DS, affecting predominantly the hippocampal body region; b) an absence of significant correlation between hippocampal volumes and memory skills in both groups; c) no difference in the 3-year trajectories of hippocampal volume change between patients and controls; d) a significant association between the size of hippocampal head volume at T1 and the presence of hallucinations at T2 within patients with 22q11DS.

The pattern of significant hippocampal reduction observed in the present study is consistent with previously reported results in the syndrome (Kates et al., 2006; Deboer et al., 2007). More specifically, the strongly significant reduction of the hippocampal body replicates our previous results in another sample of patients with 22q11DS spanning a wider age range (6–39 years old) (Debbane et al., 2006). This strengthens the hypothesis that hippocampal body reduction may be a state feature of 22q11DS. A possible etiology for the reduced hippocampal body is a deleterious effect of stress on the structure (Wang et al., 2010). Many stressors can specifically affect children with 22q11DS, including, for instance, their frequent need for cardiac or palatal surgery in early childhood or their increased frequency of infections due to thymic dysfunction (Robin and Shprintzen, 2005). The stress hypothesis is, however, not the only possible explanation for the hippocampal body reduction. The hippocampal body is connected to the parieto-lateral, posterior cingulate, retrosplenial, temporal and prefrontal cortices (Kahn et al., 2008). In 22q11DS, the parieto-lateral, the posterior cingulate and the temporal cortical structures are known to be particularly reduced. Thus, one can postulate that the most decreased part of the hippocampus reflects a reduction in the amount of input received from connected cortical regions during development. In turn, these deficient networks are expected to be responsible for poorer function.

When considering the implication of the hippocampus in memory skills, we were surprised not to find a significant correlation between any of the hippocampal subvolumes and mnesic capacities in our sample. While the posterior hippocampus is thought to be implicated in spatial memory (Moser and Moser, 1998), the body itself may play a role in delayed verbal memory processes (Chen et al., 2010). However, a recent meta-analysis on hippocampal volumes and memory skills (Van Petten, 2004) revealed contradictory correlations between performance and hippocampal volume and suggested hypotheses varying from “bigger is better” in adults to “smaller is better” in children. The present sample of children and adolescents with a diverse degree of psychotic symptomatology may be too heterogeneous to permit us to observe a linear correlation, and the variety of memory skills sustained by the hippocampus may fail to be captured by standardized memory assessments (Debbane et al., 2008).

Contrary to our expectations but similarly to the previous longitudinal findings in the syndrome (Gothelf et al., 2007), we did not detect any group difference in hippocampal volume trajectories over the 3-year interval. Structural hippocampal maturation has been shown to be complex and heterogeneous (Gogtay et al., 2006; Nugent et al., 2007). In typically developing individuals, the overall hippocampal volume is thought to remain unchanged between 4 and 25 years, because volume loss over time in the anterior parts is compensated by volume gain in the middle and posterior parts (Gogtay et al., 2006). In patients with childhood onset schizophrenia, similarly heterogeneous developmental changes have been evidenced in a sample of 29 patients who were scanned 2 to 5 times within 2-year intervals (Nugent et al., 2007). Although we used subregional analyses in order to increase our sensitivity to the heterogeneous process of hippocampal development, our study probably lacks a sufficient amount of longitudinal data to model a potential non-linear effect of age over hippocampal volume. The delineation of complex non-linear trajectories requires a very large sample size, which is unfortunately difficult to recruit in a rare disease such as 22q11DS. However, to prevent a potential non-linear age effect to bias our results, we accurately matched the age of our 22q11DS participants with the controls. We also limited the age range of our sample: whereas our initial report of hippocampal measurements in 22q11DS included participants aged up to 39 years old (Debbane et al., 2006), we only included individuals between 6 and 22 years in the present report. The absence of any observed subregional hippocampal differences between patients and controls emphasizes the need for larger sample size and increased number of time points over childhood and adulthood.

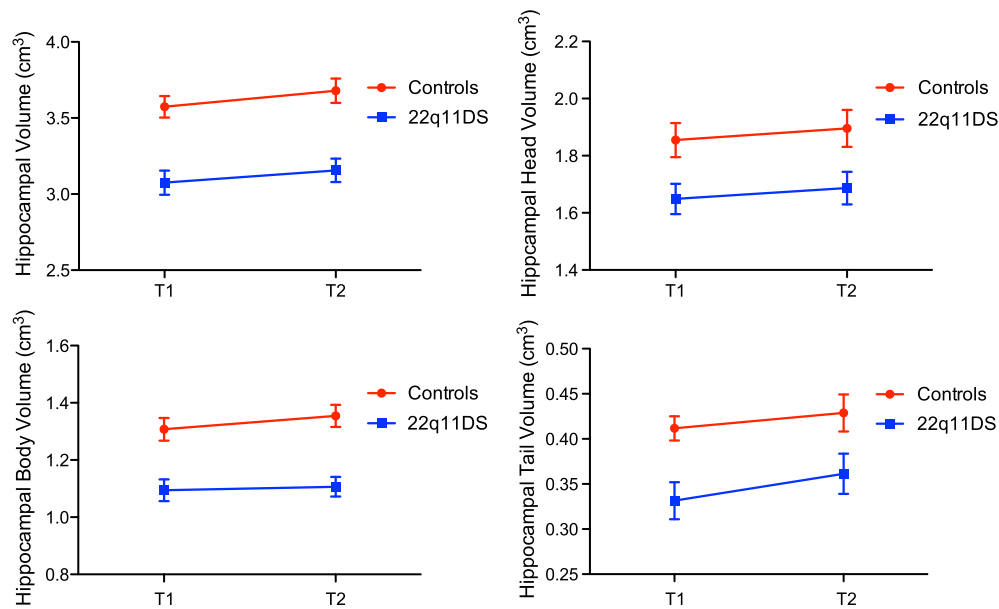


Fig. 1. Comparison of hippocampal volumes trajectories between controls and 22q11DS subjects. (mean values and SEM. For complete statistics, refer to Table 1.)

Despite the absence of divergent trajectories between groups, an aspect of our results suggests an interaction between hippocampal maturation and the emergence of hallucinations within the 22q11DS group. Using repeated-measures with hallucinations as the dependent variable, we found that a larger hippocampal head volume at T1 was a significant predictor of the development of hallucinations at T2. Whereas we could have expected the Met allele carriers to be at higher risk to develop hallucinations (Gothelf et al., 2005), our finding was statistically independent of exposure to psychotropic medication or the COMT polymorphism. The hippocampal head reciprocally connects to the amygdala (Kishi et al., 2006) and prefrontal cortex (Barbas and Blatt, 1995), where it modulates dopaminergic release (Taepavarapruk et al., 2008). In participants at ultra high risk (UHR) of developing psychosis, Phillips et al. (2002) observed a significantly smaller anterior hippocampal volume compared to controls. However, in accordance with our results, the UHR participants who later develop psychosis (i.e. the prepsychotic participants) had larger baseline size of the anterior hippocampus than UHR participants who did not go on to develop

psychotic symptoms (Phillips et al., 2002). More recently, Schobel et al. (2009) also observed that an increased basal cerebral blood volume in the CA1 subfield of the hippocampus was highly predictive of the subsequent development of a schizophrenia spectrum disorder in UHR participants (Schobel et al., 2009). Altogether, the results published by Phillips et al., by Schobel et al., and the present results all point to a role for a dysfunctional and structurally abnormal anterior hippocampus as a key marker in the emergence of schizophrenia. The biological mechanisms underlying the macroscopic changes remain largely unknown, however, as morphometric studies such as ours cannot provide information about ultrastructural parameters at the cellular or synaptic level.

In the present study, increased volume of the head of the hippocampus was specifically associated with hallucinations and not with delusions. We hypothesize that the lack of association between hippocampal head volume and delusions can be explained by the less targeted and more complex process leading to delusions. As suggested by Kapur et al. (2003), the acute onset of aberrant internal perceptions (hallucinations) precedes the long-term incorporation of these misperceptions in the personal cognitive scheme (delusions). Future studies may be required to further explore new candidates in the search for symptom-specific brain biomarkers associated with the development of schizophrenia spectrum disorder.

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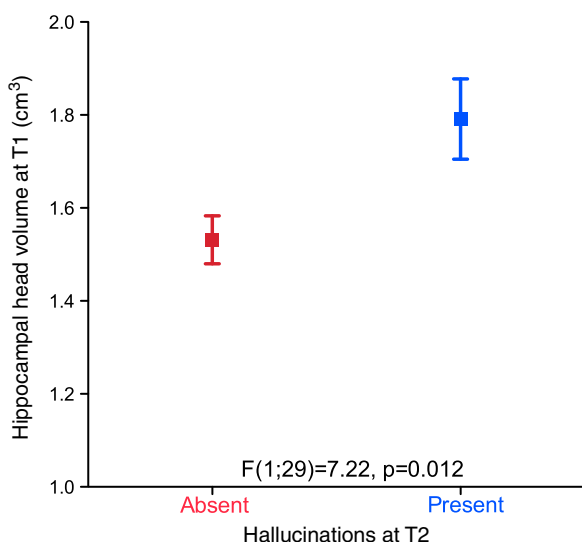


Fig. 2. Larger hippocampal head volume at T1 is associated with presence of hallucinations at T2 among subjects with 22q11DS (mean values and SEM).

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