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Reference

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ARTICLE

Positive psychotic symptoms are associated with divergent developmental trajectories of hippocampal volume during late adolescence in patients with 22q11DS

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Abstract

Low hippocampal volume is a consistent finding in schizophrenia and across the psychosis spectrum. However, there is a lack of studies investigating longitudinal hippocampal development and its relationship with psychotic symptoms. The 22q11.2 deletion syndrome (22q11DS) has proven to be a remarkable model for the prospective study of individuals at high risk of schizophrenia to unravel the pathophysiological processes predating the onset of psychosis. Repeated cerebral MRIs were acquired from 140 patients with 22q11DS (53 experiencing moderate-to-severe psychotic symptoms) and 135 healthy controls aged from 6 to 35 years and with up to 5 time points per participant. Hippocampal subfield analysis was conducted using FreeSurfer-v.6 and FIRST-FSL. Then, whole hippocampal and subfield volumes were compared across the groups. Relative to controls, patients with 22q11DS showed a remarkably lower volume of all subfields except for CA2/3. No divergent trajectories in hippocampal development were found. When comparing patients with 22q11DS exhibiting psychotic symptoms to those without psychosis, we detected a volume decrease during late adolescence, starting in CA1 and spreading to other subfields. Our findings suggested that hippocampal volume is consistently smaller in patients with 22q11DS. Moreover, we have demonstrated that patients with 22q11DS and psychotic symptoms undergo a further decrease in volume during adolescence, a vulnerable period for the emergence of psychosis. Interestingly, CA2/3, despite being affected in patients with psychotic symptoms, was the only area not reduced in patients with 22q11DS relative to controls, thus suggesting that its atrophy exclusively correlates with the presence of positive psychotic symptoms.

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Introduction

It is widely acknowledged that the hippocampus plays a crucial role in learning, memory retrieval and imagination [1]. Beyond its involvement in memory, converging lines of evidence supported by MRI [2–7] and postmortem studies [8, 9] has suggested that patients with schizophrenia are characterized by a smaller hippocampus. In fact, a lower hippocampal volume has been found in patients across the psychosis spectrum [3, 10, 11], comprising first-episode psychosis patients (FEP) [12, 13] and subjects at high/ultrahigh (UHR) risk for psychosis [14, 15]. However, a meta-analysis has recently shown that there was no evidence for a significant reduction in the whole hippocampal volume in patients at clinical high risk for psychosis [16], suggesting that only subtler changes might be detectable early in disease progression. Indeed, a dose-response relationship depending on the stage of the disease has been found in individuals at UHR for psychosis [10].

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To date, many studies have reported the involvement of different combinations of hippocampal subfields—CA1, CA2/3, CA4, dentate gyrus and subiculum—in patients with clinical high risk for psychosis [12, 17, 18]. Consequently, several theories aimed at explaining the relationship between psychotic symptoms and hippocampal volume reduction have devoted great attention to the functional anatomy of the hippocampus [19]. In fact, each hippocampal subfield has a different density of pyramidal neurons [20], diverse synaptic architecture and distinct patterns of connectivity with cortical areas [21]. Notably, dentate gyrus, CA3 and CA1 are part of the trisynaptic circuitry responsible for encoding episodic memory [22], whereas the subiculum extends the persistence of such information conveying it to the neocortex [23].

Even though there is no consensus on which subfield is central to the development of psychosis, CA3 and CA1 are very likely to be involved [24].

One theory posits that CA3 hyperactivity is instrumental to the onset of psychotic symptoms [25]. CA3 has a pivotal role in the hippocampal autoassociative network responsible for memory encoding and retrieval [26], so it might be involved in the generation of false memories, perceived as hallucinations by schizophrenic patients [25, 27].

On the other hand, CA1 appeared to be the earliest affected area in UHR [28, 29] and FEP [18] patients. One study demonstrated that increased cerebral blood volume (CBV) in the left CA1 of UHR patients predicted its atrophy and the development of psychosis [28]. Similarly, in mouse models of ketamine-induced schizophrenia, CA1 exhibited the highest CBV, paralleled by an increase in extracellular glutamate concentration [30]. Therefore, elevated hippocampal activity and subsequent excitotoxicity might have a mechanistic role in the development of atrophy [31]. Finally, another study showed that UHR patients who developed schizophrenia had, at the first assessment, a lower right hippocampal and CA1 volume and a steeper CA3 volume decline over time [29], suggesting that CA1 and CA3 might have different roles in the development of psychosis.

Overall, a volume decrease in specific subfields has been demonstrated cross-sectionally [10–12, 15] and longitudinally [13, 14, 29, 30] in patients at clinical risk of psychosis. Subjects with a genetic risk, such as siblings of psychotic patients, also presented hippocampal abnormalities [32–36], and hippocampal volume was demonstrated to be highly heritable [37]. Therefore, lower hippocampal volume is considered to be a putative endophenotype for psychosis [38].

However, even though the clinical high risk phase of psychosis has been extensively studied, there is a lack of studies investigating the previous period [11], i.e., that premorbid phase when possible brain dysfunctions are not yet accompanied by overt symptoms [39]. It is still debated as to whether a lower hippocampal volume is a cause or a consequence of psychotic symptoms [11], or whether this relationship is even more complex, with psychosis and volume decreases being bounded by reciprocal causation. In this regard, the study of populations with a genetic risk of psychosis provides a unique opportunity to evaluate patients from childhood to clarify the temporal relationship between hippocampal development and the onset of psychosis.

The 22q11.2 deletion syndrome (22q11DS)—a neurodevelopmental disorder caused by a 1.5-3 Mb deletion on the long arm of chromosome 22—is considered to be among the most important genetic risk factors for psychosis [40]. As up to 41% of patients with 22q11DS will develop a psychotic disorder by adulthood [41], the syndrome has been recognized as a valuable model for detecting early psychosis biomarkers. Furthermore, predictive measures of conversion to psychosis, such as UHR status, have been validated in patients with 22q11DS [42]. Deletion carriers have cognitive and learning deficits and are more prone to developing psychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), anxiety and obsessive-compulsive disorder (OCD) [43]. A wide range of medical conditions, including congenital heart defects (CHD) and T-cell immunodeficiency, can accompany neuropsychiatric manifestations [43]. Brain abnormalities are also a common feature of the syndrome, as patients have an average 11% total brain volume decrease [44] and reduced gyrification in the frontal and parietal lobes [45]. Moreover, lower hippocampal volume—either driven by the hippocampal head [46] or body [47–49]—has been found [50], and the size of the hippocampal head has been positively correlated to the onset of hallucinations [49]. However, it remains unclear at which point during development the hippocampal volume of patients with 22q11DS diverges from healthy subjects, i.e., if hippocampal volume is already reduced in patients during childhood or whether it occurs later, during adolescent brain maturation.

Consequently, the first objective of the present study was to investigate the developmental trajectory of hippocampal volume in a large cohort of patients with 22q11DS over a wide timespan using a longitudinal design. The second aim was to analyze the association between hippocampal development and the onset of positive psychotic symptoms. A longitudinal approach was chosen to provide insights into whether a smaller hippocampus at baseline and/or a further volume decrease is specific to 22q11DS patients experiencing symptoms of psychosis.

We employed a recently developed automated segmentation technique from FreeSurfer v6.0, which allows a better delineation of the hippocampal subfields [51] than its previous version [52]. Furthermore, given previous studies highlighting the existence of selective morphological

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abnormalities in the anterior and mid-body hippocampus across the psychosis spectrum [7, 13, 15, 53] and in patients with 22q11DS [46–49], we complemented the analysis of subfields with FIRST-FSL [54], another widely used technique, which provides information about the shape of the hippocampus along the anteroposterior axis.

According to previous studies [46–50], we hypothesized that by using these techniques, we would detect a global and robust difference between patients with 22q11DS and healthy controls. In light of the findings reported with UHR patients [10, 13, 14, 29], we further proposed that 22q11DS patients with moderate-to-severe psychotic symptoms would have a volume reduction in critical subfields, such as CA1 and CA3. Understanding the timing of hippocampal development in patients with 22q11DS could help to predict the emergence of psychotic symptoms in at-risk populations.

Materials and methods

Participants

One hundred forty individuals with a genetically confirmed diagnosis of 22q11DS and 135 healthy controls (HC) were recruited in the context of an ongoing longitudinal study being carried out in Geneva since 2001 (additional details in Supplementary Information and Supplementary Table 1).

The age of the patients and HC ranged from 6 to 35 years, and the two groups were matched for age and sex. On average, each participant was assessed at 2.14 time points, which varied from 1 to 5 across participants (Table 1). The presence of axis I disorders according to DSM-IV criteria and current use of psychotropic medication in the group of patients with 22q11DS are listed in Table 2.

Written informed consent was obtained from participants and/or their parents. The study was approved by the cantonal ethics committee and conducted according to the Declaration of Helsinki.

Psychiatric assessment

Patients with 22q11DS experience subthreshold psychotic symptoms to a greater extent than the general population; [55] therefore, they are a compelling model to explore the underlying neurobiology. The presence of moderate-to-severe psychotic symptoms was assessed at each time point by means of the Structured Interview for Psychosis-Risk Syndromes (SIPS), as the SIPS is a well-validated diagnostic tool for assessing psychotic symptoms in deletion carriers [56, 57]. Patients with 22q11DS were categorized as experiencing positive symptoms of psychosis, using a cutoff score of 3 or higher in at least one of the corresponding items. Together with time and frequency criteria, this intensity threshold has been proven by several studies to be the most sensitive at detecting prodromal risk syndromes [58]. Negative symptoms of psychosis, with a score of 3 or higher in at least one negative SIPS subscale, were taken into account separately to enable clarification of the relative contribution of positive and negative symptoms to hippocampal development.

Due to their young age, 33 patients were unable to complete the SIPS, thus reducing the sample group to 107 patients. Negative symptoms were present in 72 patients, while positive symptoms were present in 52 patients, including 13 with a diagnosis of schizophrenia and 2 with schizoaffective disorder. Specifically, 15 patients had a score of 6 on one or more positive subscales at one or more time points.

The inclusion of a heterogeneous group of deletions carriers with various degrees of positive psychotic symptoms allowed us to compare larger subgroups to discover putative brain abnormalities underlying the presence of such symptoms. From now onwards, all the patients with moderate-to-severe positive psychotic symptoms will be referred to as 22q11DS psy+ patients.

MRI acquisition

Due to the wide timespan of this study, the scans were acquired with three different scanners: a 1.5T Philips Intera scanner was used for the first 151 scans, a 3T Siemens Trio for the subsequent 294 scans and a 3T Siemens Prisma for the remaining 138 scans. T1-weighted images were acquired at the Center for Biomedical Imaging (CIBM) in Geneva with a three-dimensional volumetric pulse. The 1.5T scanner parameters were TR = 35 ms, TE = 6 ms, flip angle = 45°, NEX = 1, matrix size = 256 × 192, field of view = 24 cm2, slice thickness = 1.5 mm, 124 slices. The parameters for both 3T scanners were TR = 2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 × 256, field of view = 23.5 cm, slice thickness = 3.2 mm, and 192 slices.

To avoid possible confounding factors, the scanner model was entered as a covariate in all the statistical analyses.

T1-weighted images underwent fully automated image processing with FreeSurfer version 5.3.0, comprising skull stripping, intensity normalization, reconstruction of the internal and external cortical surface and parcellation of subcortical brain regions [59].

Hippocampal segmentation

A recently developed automated segmentation technique published with FreeSurfer version 6.0 was used to label the

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Table 1 Demographic information

	22q11DS patients	Healthy controls	T-test/ Chi square
Number of subjects (female%)	140 (51.4%)	135 (48.1%)	$p = 0.934$
Number of subjects with 5 visits	8	3	$p = 0.124$
Number of subjects with 4 visits	16	11	$p = 0.313$
Number of subjects with 3 visits	21	19	$p = 1.000$
Number of subjects with 2 visits	42	47	$p = 0.613$
Number of subjects with 1 visit	57	65	$p = 0.785$
Number of scans (total)	308	275	N/A
Number of 1.5 T scans	71	80	$p = 0.09$
Number of 3 T (Trio) scans	162	132	$p = 0.23$
Number of 3 T (Prisma) scans	75	63	$p = 0.75$
Age range	6–35 y.o.	6–35 y.o.	N/A
Mean age	16.24 ± 6.44	15.48 ± 5.87	$p = 0.089$
Mean age at first visit	13.53 ± 6.44	13.26 ± 5.33	$p = 0.713$
Mean distance between visits	3.80 ± 1.07	3.72 ± 1.55	$p = 0.724$

Table 2 Medical history comprising psychiatric disorders and medications in the whole group of patients with 22q11DS and in the subgroups with and without SIPS positive score > 3

	All 22q11DS	22q11DS SIPS positive > 3	22q11DS SIPS positive < 3	*p*-value
Number of subjects (%f)	140 (51.4%)	53 (50.94%)	54 (48.15%)	0.7725
Mean age	16.33 ± 6.44	17.64 ± 6.25	17.43 ± 6.18	0.7882
Number of scans (total)	308	134	125	N/A
Number of 1.5 T scans	71	33	27	0.564
Number of 3 T (Trio) scans	162	72	70	0.7139
Number of 3 T (Prisma) scans	75	29	28	0.883
Subjects medicated	67 (47.85%)	32 (60.38%)	26 (48.15%)	0.0767
Methylphenidate	37 (26.43%)	12 (22.64%)	17 (31.48%)	0.2089
Antidepressants	26 (18.57%)	14 (26.41%)	9 (16.7%)	0.0728
Antipsychotics	15 (10.71%)	15 (28.3%)	0	<0.001
Anxiolytics	17 (12.14%)	10 (18.87%)	6 (11.11%)	0.0742
Antiepileptic drugs	7 (5%)	4 (7.55%)	3 (5.56%)	0.5210
More than one class of medication	21 (15%)	13 (24.53%)	7 (12.96%)	0.0120
Subjects meeting criteria for psychiatric diagnosis	97 (69.28%)	45 (84.9%)	33 (61.11%)	0.0010
ADHD	52 (37.14%)	24 (45.28%)	20 (37.04%)	0.2153
Anxiety disorders	46 (33.57%)	23 (42.59%)	17 (31.48%)	0.0784
Mood disorders	28 (20%)	13 (24.53%)	9 (16.67%)	0.1266
Psychotic disorders	20 (14.28 %)	20 (37.75%)	0	<0.001
OCD	12 (8.57%)	4 (7.55%)	3 (5.56%)	0.5210
More than one diagnosis	40 (28.57%)	22 (41.51%)	13 (24.07%)	0.0025

NB: due to the lack of SIPS data in younger patients, the sum of the two sub-groups does not correspond to the whole group

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hippocampal subfields. This algorithm employs a probabilistic atlas built from a combination of ex vivo 7T MRI data from autopsied brains and in vivo 3T images of the neighboring structures in a Bayesian framework [51]. Compared to the previous version [52], this technique provides a higher resolution and the segmentation of a larger number of structures, including the *cornu ammonis* regions (CA1, CA2/3, CA4 and their molecular layer (ML)), the granule cell layer of dentate gyrus (GC-DG), the hippocampal tail and fissure. Surrounding regions, such as subiculum, parasubiculum, presubiculum, the hippocampus-amygdala-transition-area and fimbria, are also

included. Given the purpose of the present study, the volume of the whole hippocampus and 7 relevant subfields, CA1, CA2/3, CA4, GC-DG, ML, tail and subiculum, were analyzed. For an example of FreeSurfer segmentation in a patient and an HC, see Fig. 1.

Because we used FreeSurfer v5.3 to preprocess the data and v6.0 to perform hippocampal subfield segmentation, we tested and confirmed the reliability of using different versions of FreeSurfer by means of intraclass correlation coefficient analysis (Supplementary Table 5).

To understand whether the difference between patients with 22q11DS and HC has a specific distribution along the anteroposterior axis, a shape analysis via the FSL software FIRST [54] was also performed. This technique provides a surface mesh of the hippocampus for each subject in a common 3D space, modeled on intensity distribution and vertex analysis. Then, an average mask was created by concatenating all the hippocampal meshes of patients with 22q11DS and controls.

All the obtained images were visually inspected and then excluded from the analysis if the quality of the segmentation was inappropriate. Specifically, we carefully checked in each subject that the hippocampal mask as whole was correctly placed, with no portions of the hippocampus were cut off or shifts of the mask beyond the borders of the hippocampus. Then, we verified that there were no mislabeling of hippocampal subfields and extrahippocampal regions; in this regard, as suggested by the quality control procedure provided by the ENIGMA protocol (https://pgcptsd.com/wpcontent/uploads/2017/08/PTSD_Instructions_Subfields_part_IR_II.pd), any mislabeling of single subfields was sufficient to exclude the whole segmentation. We therefore excluded 2 scans of patients with 22q11DS from FreeSurfer segmentation and 5 scans (3 patients and 2 controls) from FIRST-FSL analysis.

Statistical analyses

Mixed modeling has proven to be an ideal method for handling nested data, such as multiple time points [60]. Considering that participants had a variable number of time points, with an inconstant time interval and age distribution (Supplementary Fig. 1), a mixed model regression analysis, described in previous papers [61, 62], was used to analyze the longitudinal data from FreeSurfer. Briefly, population parameters (age and diagnosis) were modeled as fixed effects and within-subject factors as random effects by using the nlmefit function in MATLAB R2017a (MathWorks). The normal distribution of data in each group was required and therefore evaluated by our statistical analysis approach. Total intracranial volume, sex, scanner model and antipsychotic medications were included as covariates. Developmental trajectories were estimated by fitting random-slope models (constant, linear, quadratic or cubic, each corresponding to a different relationship between age and hippocampal volume) to our data, taking into account both within-subject and between-subject effects. Then, the most suitable model order was selected using the Bayesian information criterion, obtaining, e.g., a full quadratic model as follows:

$$Y_{ij} = \beta_0 + \beta_{g1} \cdot g_i + \beta_{a1} \cdot a_{ij} + \beta_{ag1} \cdot g_i \cdot a_{ij} + \beta_{a2} \cdot a_{ij}^2 + \beta_{ag2} \cdot g_i \cdot a_{ij}^2 + u_{i0} + u_{i1} \cdot a_{ij} + \epsilon_{ij}$$

$$\begin{aligned} Y &: hippocampal\ volume \\ i,j &: [subjects, scan]index \\ \beta_{xn} &: fixed\ effects \\ g &: grouping\ variable \\ a &: age \\ u &: normally\ distributed\ random\ effect \\ \epsilon_i &: normally\ distributed\ error\ term \end{aligned}$$

The significance of the between-group differences in the intercept and in the slope were evaluated by means of a log-likelihood ratio test between the full model and any of the following reduced models:

Reduced group effect model

$$Y_{ij} = \beta_0 + \beta_{a1} \cdot a_{ij} + \beta_{a2} \cdot a_{ij}^2 + u_{i0} + u_{i1} \cdot a_{ij} + \epsilon_{ij}$$

Reduced slope model

$$Y_{ij} = \beta_0 + \beta_{g1} \cdot g_i + \beta_{a1} \cdot a_{ij} + \beta_{a2} \cdot a_{ij}^2 + u_{i0} + u_{i1} \cdot a_{ij} + \epsilon_{ij}$$

Hence, we obtained a comparison between the intercept (group effect) and the slope of developmental trajectories (group × age interaction effect) of the hippocampal volume of each group. Finally, the results were adjusted for multiple testing with the false discovery rate correction. Where appropriate (i.e., in quadratic models), the age corresponding to the inflection point of each developmental trajectory was estimated at the intersection between the derivative of the curve in that point and the x-axis.

We further tested whether the degree of psychotic symptoms as measured by the SIPS for each positive subscale (P1: unusual thought content/delusional ideas, P2: suspiciousness/persecutory ideas, P3: grandiose ideas, P4: perceptual abnormalities/hallucinations, P5: disorganized communication) was correlated with hippocampal volume in patients with 22q11DS by using the fitlme function in MATLAB R2017a (MathWorks). The results were covaried for age, age^2, sex, ICV, antipsychotics and scan type and finally adjusted for multiple comparisons with FDR correction.

FSL data were analyzed cross-sectionally, selecting the first time point for each participant. Statistical maps and analyses were included in FIRST-FSL and obtained following the pipeline described on the FSL website (https://

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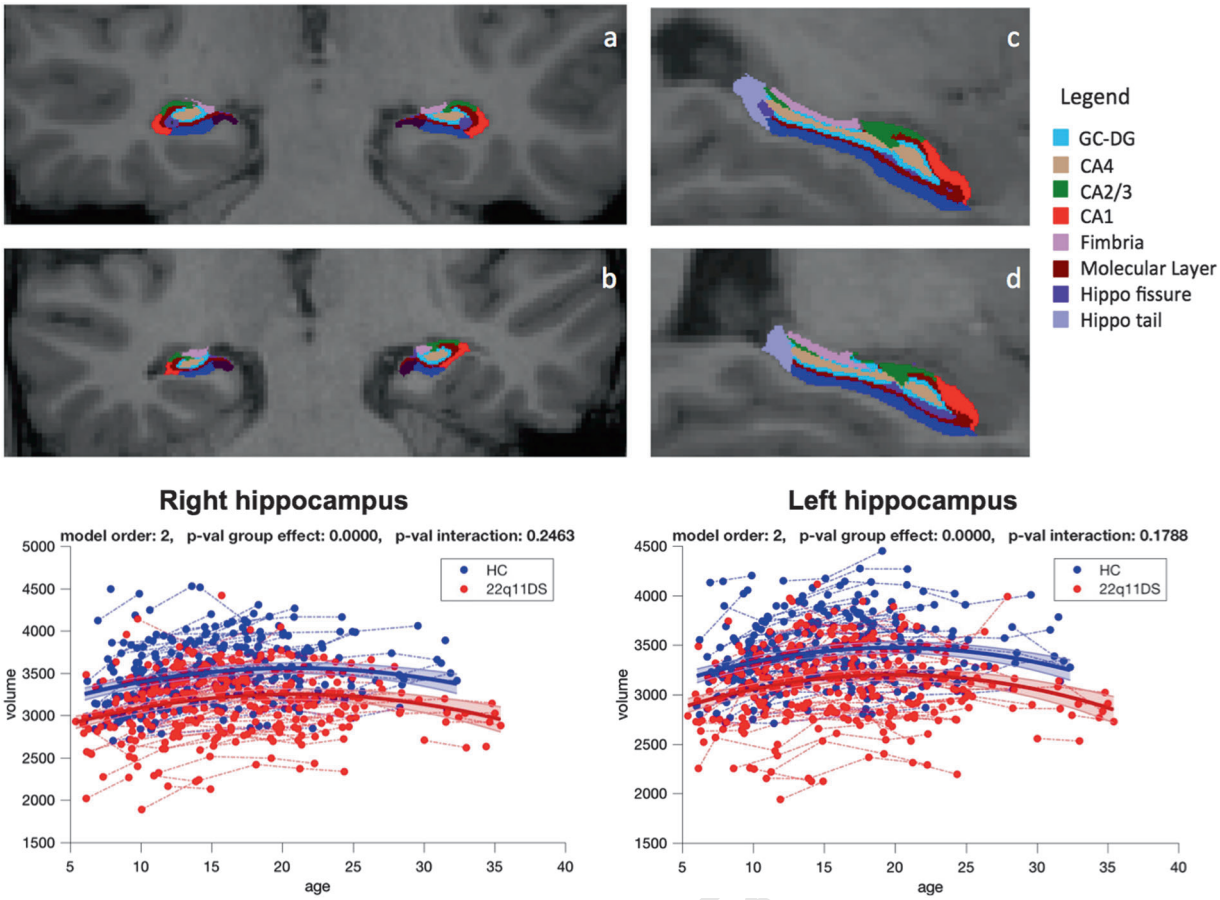

Fig. 1 Comparison between patients with 22q11Ds and HC. Upper panel: an example of Freesurfer v.6.0 hippocampal segmentation with coronal (**a**, **b**) and sagittal (**c**, **d**) sections in a healthy control (**a**, **c**) and in a patient with 22q11DS (**b**, **d**) of the same age. Lower panel: mixed model analysis of the developmental trajectories showing a marked smaller hippocampal volume in patients with 22q11DS without differences in the shape of the two curves

fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide). With the 'randomise' function, significant differences between the two groups were computed with a cluster-based multiple-comparison correction, covarying for total intracranial volume, sex, scanner model, age and antipsychotic medications. The output was a 3D mask showing a selective inward or outward displacement in the affected regions, depending on whether the hippocampus of the patients was smaller or larger than the controls.

Results

Patients with 22q11DS have widespread reductions in hippocampal volume

A smaller hippocampal volume was demonstrated bilaterally in patients with 22q11DS in comparison to HC by using data from FreeSurfer and FIRST-FSL segmentations.

The mixed model analysis revealed strong group differences in the whole right and left hippocampal volume ($p < 0.001$), with no difference in developmental trajectories (Fig. 1). Similarly, a consistently lower volume was detected bilaterally in all subfields ($p < 0.001$), except for CA2/3 (Table 3). As in a previous study on healthy participants [63], all the trajectories had a second-order model, meaning that the relationship between age and hippocampal volume was quadratic (Fig. 2).

The statistical map obtained using FIRST-FSL confirmed a diffuse inward displacement in the hippocampus of patients with 22q11DS involving the head, the body and the tail of the hippocampus. In particular, the medial and lateral surfaces of the right and left hippocampi were more consistently affected, whereas the upper and lower hippocampal surfaces showed some unaffected areas along the midline, irrespective of anatomical boundaries (Fig. 3).

22q11DS psy+ patients have altered developmental trajectories of specific hippocampal subfields

To further assess the association between the development of hippocampal volume and psychotic symptoms,

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Table 3 Results of the mixed-model analysis of the longitudinal volumetric comparison in 22q11DS and HC (left) and in 22q11DS patients with and without positive (center) and negative (right) psychotic symptoms

		22q11DS patients vs HC			SIPS positive symptoms			SIPS negative symptoms		
		Model order	*p*-value group effect	*p*-value interaction	Model order	*p*-value group effect	*p*-value interaction	Model order	*p*-value group effect	*p*-value interaction
Whole	Left	2	<0.001	0.1788	2	0.0035	0.9481	2	0.4426	0.2647
	Right	2	<0.001	0.2463	2	0.0020	0.0054	2	0.2793	0.2657
Subiculum	Left	2	<0.001	0.2206	2	0.0114	0.4436	2	0.5947	0.3988
	Right	2	<0.001	0.0994	2	0.0900	0.2322	2	0.2260	0.1974
CA1	Left	2	<0.001	0.3251	2	0.0065	0.8213	2	0.7209	0.5478
	Right	2	<0.001	0.7646	2	0.0535	0.0574	2	0.2294	0.3190
CA2/3	Left	2	0.3554	0.7290	2	0.0179	0.8566	2	0.4540	0.2767
	Right	2	0.0470	0.6536	2	0.0035	0.0063	2	0.1311	0.2739
CA4	Left	2	<0.001	0.2197	2	0.0126	0.7546	2	0.1541	0.0760
	Right	2	<0.001	0.9006	2	0.0022	0.0024	2	0.2362	0.4083
GC-DG	Left	2	<0.001	0.1667	2	0.0136	0.9187	2	0.2106	0.1148
	Right	2	<0.001	0.7589	2	0.0023	0.0028	2	0.2387	0.3901
Molecular layer	Left	2	<0.001	0.2253	2	0.1183	0.6901	2	0.2365	0.6374
	Right	2	<0.001	0.7880	2	0.1125	0.0633	2	0.2396	0.1986
Tail	Left	2	<0.001	0.9312	2	0.0736	0.4467	2	0.9263	0.8581
	Right	2	<0.001	0.0143	2	0.0537	0.0721	2	0.8912	0.9998

Model order refers to the order of the function that optimally fitted the developmental data; in this case, it is a quadratic function. *p*-value group effect evaluates the mean volume difference between the two groups, while *p*-value interaction refers to the difference in the shape of the developmental trajectory. The significance threshold was set at 0.05; all the *p*-values are corrected for multiple comparisons with the false discovery rate correction. Subfields volumes values for each group are reported in mm^3 with standard deviation

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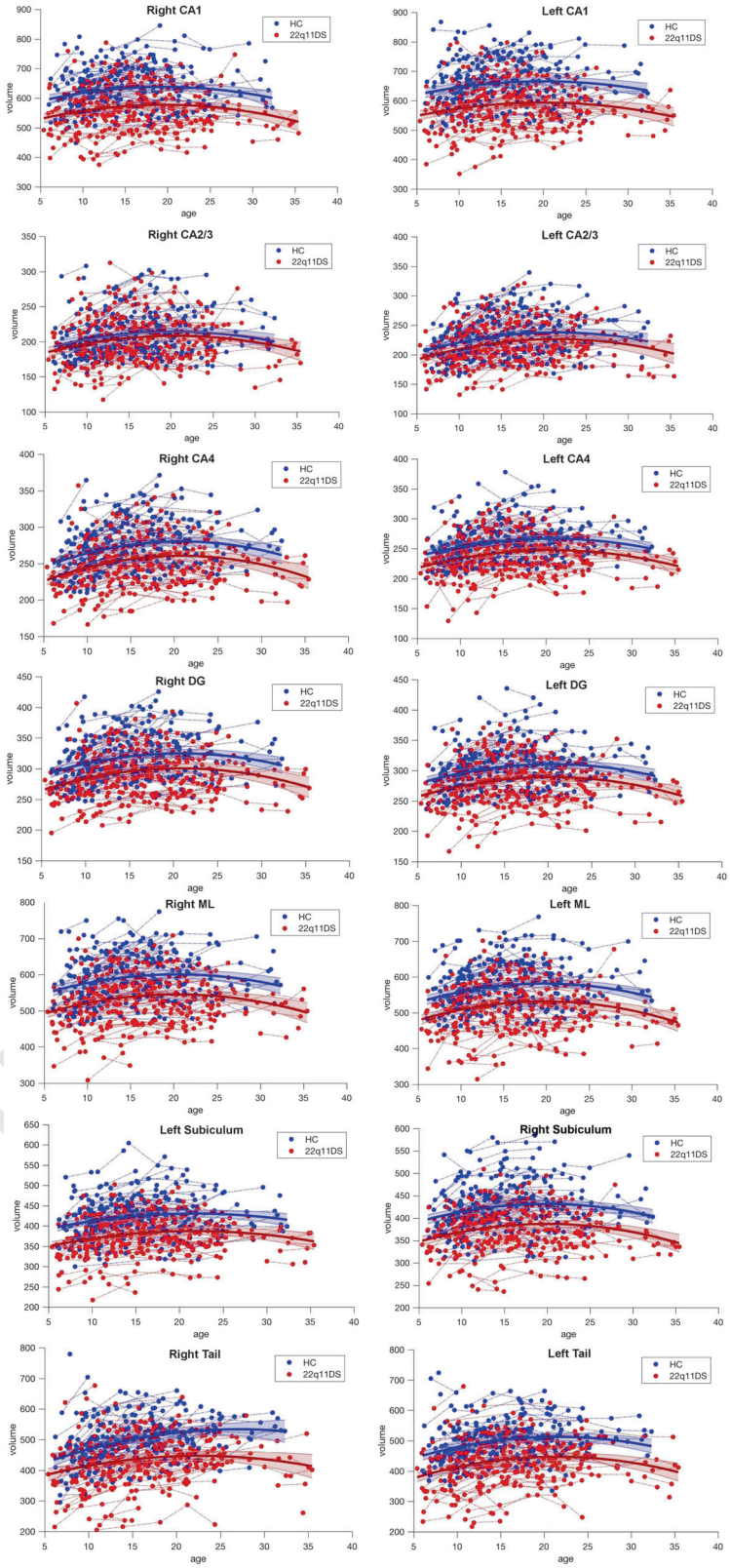

Fig. 2 . Developmental trajectories of hippocampal subfields in patients with 22q11DS and HC

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patients with moderate-to-severe positive or negative symptoms were compared to patients with low symptom scores.

The hippocampal volume of participants with at least one SIPS negative symptom score ≥3 did not differ from the group without negative symptoms (Table 3). In contrast,

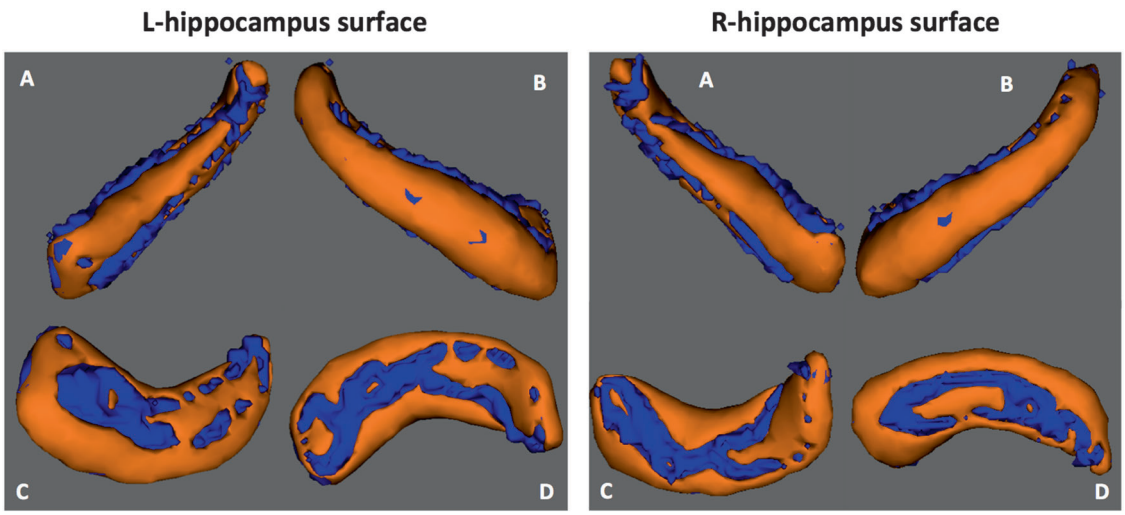

Fig. 3 Results of FIRST-FSL vertex analysis of group differences between patients with 22q11DS and HC. The orange overlay indicates the hippocampal regions displaying significant inward displacement in patients with 22q11DS. **a** medial surface; **b** lateral surface; **c** upper surface; **d** bottom surface

22q11DS psy+ patients had a decreased hippocampal volume ($p = 0.002$ on the right side and $p = 0.0035$ on the left side) (Fig. 4) compared to patients without positive symptoms. Moreover, 22q11DS psy+ patients had lower volumes of distinct subfields: bilateral CA2/3, CA4 and GC-DG and left CA1 and subiculum (Table 3). The right CA1 approached significance ($p = 0.053$).

Slope differences were only detected for the right hippocampus, with a developmental trajectory showing a volume decrease starting from 18.5 years in 22q11DS psy+ patients (Supplementary fig. 4). Right-side subfields displayed similar developmental trajectories across subfields with an inflection point corresponding to late adolescence: CA1: 16.5 years, DG: 17.3 years, CA4: 18 years, CA2/3: 18.8 years (Supplementary Fig. 2).

22q11DS patients with hallucinations have aberrant developmental trajectories

We evaluated whether hallucinations as measured by SCID-I or DICA (see Supplemental Information and specifically Supplementary Table 2 for further details) were specifically associated with a decreased hippocampal volume. Patients with 22q11DS who experienced hallucinations had a bilaterally reduced volume of the whole hippocampus and of all the subfields, except for the left tail, in comparison to those without hallucinations. Regarding all the right-side subfields, except for CA1 and GC-DG, 22q11DS patients with hallucinations exhibited a significantly different interaction effect (Supplementary Fig. 3), comparable to that found in the group of patients selected according to SIPS score.

The degree of positive symptoms is not correlated with hippocampal volume

We did not find a significant correlation between any of the positive SIPS subscales and volume of the hippocampal subfields (Supplementary Table 3). Only the correlation with the P5 subscale (disorganized communication) approached significance (left hippocampus $p = 0.06$, $R = -0.247$; right hippocampus $p = 0.06$, $R = -0.217$).

22q11DS patients with CHD have a smaller hippocampus

The 22q11DS patients with major CHD who underwent heart surgery (22q11DS CHD+) had a smaller hippocampus than those without cardiac malformations (see Supplementary Table 4 for demographic information in the two groups). All the subfields, except for CA2/3, were bilaterally decreased in 22q11DS CHD+. No interaction effect was detected, except for the right CA2/3. The left CA2/3 area did not show a group or interaction effect (Supplementary Fig. 4).

Discussion

A smaller hippocampal volume is an anatomical trait of patients with 22q11DS

Our findings pointed to a smaller global hippocampal volume in patients with 22q11DS than HC, broadening the evidence of a reduced hippocampal head [46] and body [47–49] previously demonstrated in smaller samples.

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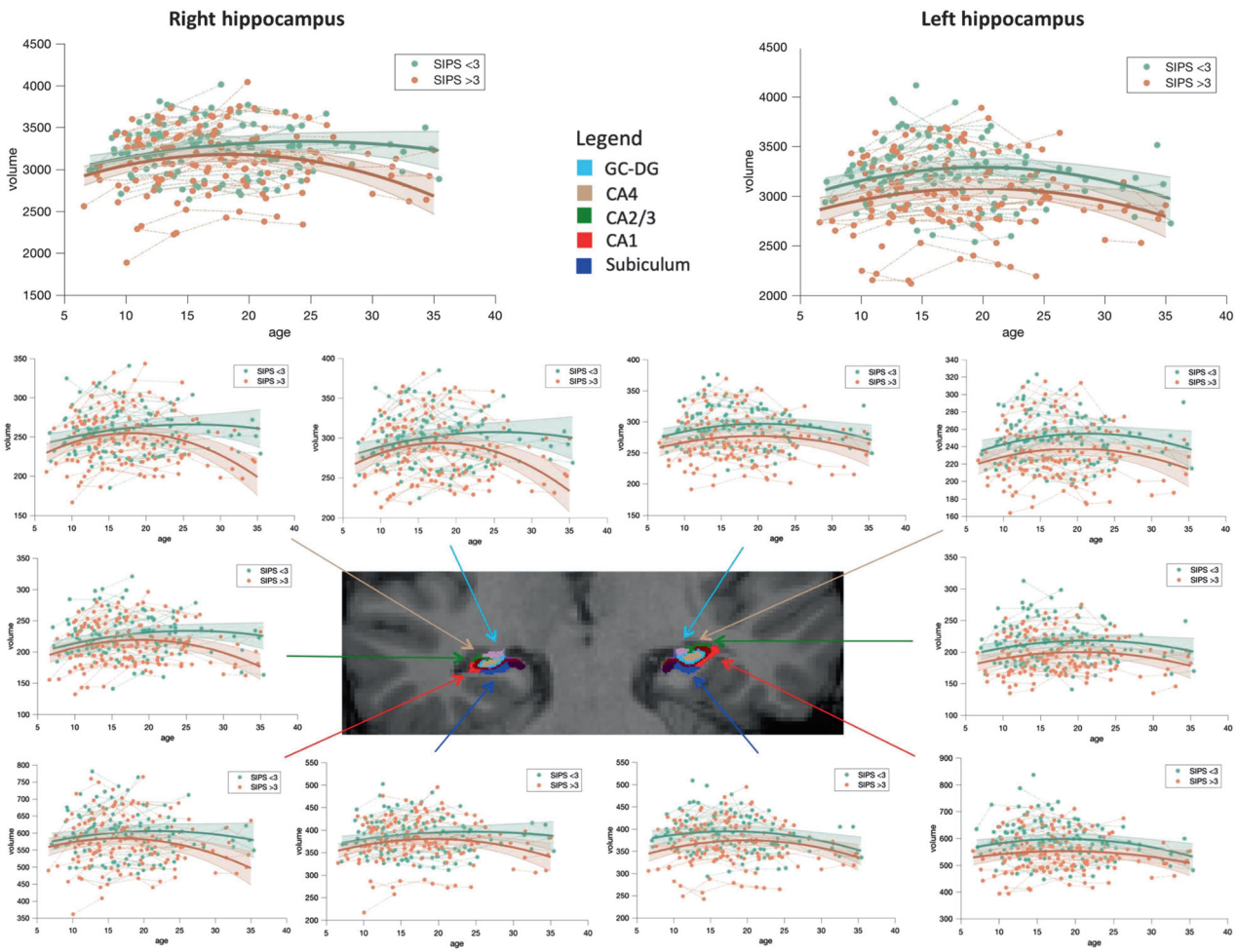

Fig. 4 Comparison between developmental trajectories of 22q11DS psy+ and psy- patients. Upper panel: developmental trajectories of the whole right and left hippocampal volume. Lower panel: each arrow specifies the subfield showed in the plot according to the color displayed in the legend

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According to the FIRST-FSL shape analysis, a significant volumetric difference without an anteroposterior gradient was detected, thus confirming a diffuse volume reduction in the group of patients with 22q11DS. Our results are therefore in line with previous MRI studies demonstrating a lower hippocampal volume in nonsyndromic UHR patients [14] and healthy relatives of schizophrenic patients [32, 33].

Similarly, all the subfields displayed a consistently smaller volume except for CA2/3. The reason why CA2/3 is the only subfield that was not affected remains elusive. However, from the observation that CHD could influence hippocampal volume in 22q11DS [64], we can formulate some hypotheses. CA3 is the most ischemia-resistant area in the hippocampus because of its more efficient vascularization, provided by the large dorsal intrahippocampal arteries [65]. If CHD had a pivotal role in determining a smaller hippocampal volume in 22q11DS, then CA3 vascularization would be a protective factor towards hypoperfusion due to hemodynamic instability. Our data partially support this hypothesis, as all the subfields, except for CA2/3, were bilaterally reduced in 22q11DS patients with CHD. Moreover, one study employing magnetic resonance angiography reported hypoplasia of the right posterior cerebral artery (PCA) in more than half of a sample of patients with 22q11DS [66]. Notably, PCA is the major source of hippocampal vascularization [65], so minor vascular anomalies might explain why the whole group of patients with 22q11DS had a smaller hippocampal volume than the HC group.

In patients with 22q11DS, the whole hippocampus and its subfields showed no divergent volume trajectories. Hence, a lower hippocampal volume already characterized the group of patients from the age of 6. Developmental studies on healthy subjects have documented that the most significant increase in hippocampal volume occurs during the first years of life [67], especially between the ages of 1 and 2 [68], while from 4 to 25 years of age, no global volume change was detected [69]. Likewise, the notion of

adult hippocampal neurogenesis in humans has recently been disputed [70]. Unfortunately, the timespan of our longitudinal dataset starts from the age of 6, so we cannot exclude a different maturation of the hippocampus before this period. However, patients with 22q11DS are known to carry a wide range of brain abnormalities with prenatal origin, such as cortical folding alterations [45]. A recent study posits the DGCR2 gene, located in the 22q11.2 region, as a pivotal regulator of early stages of corticogenesis in utero [71], implying early embryonic pathological processes conferring vulnerability to schizophrenia. Interestingly, even TBX1, another gene haploinsufficient in 22q11DS and related to CHD, can alter proper neuronal migration and disrupt corticogenesis [72]. However, CHD could have alternatively acted through hemodynamic mechanisms, since the presence of CHD in fetuses inhibited the autoregulation mechanism aimed at maintaining constant cerebral perfusion [73].

In conclusion, we demonstrated a consistently lower hippocampal volume from the age of 6 in patients with 22q11DS, which might, therefore, be an anatomical trait of the syndrome. The results with those with CHD offer exploratory evidence for the role of cardiovascular anomalies in determining a smaller hippocampal volume, presumably during corticogenesis.

22q11DS psy+ patients have a further hippocampal volume decrease in specific subfields

We observed that positive but not negative psychotic symptoms are related to a smaller hippocampal volume in patients with 22q11DS. Regarding positive symptoms, several studies have demonstrated a correlation with decreased hippocampal volume [74–77]. However, the results have been conflicting with regard to negative symptoms [17, 74, 78]. This lack of an association between hippocampal volume and negative symptoms could depend on the absence of shared pathophysiological mechanisms involving the hippocampus or on confounding factors peculiar to our sample, such as the high rate of psychiatric comorbidities.

Strikingly, CA2/3 was the only hippocampal subfield that did not differ in the group of 22q11DS psy+ patients when compared with HC, but CA2/3 underwent progressive atrophy in the patients. As such, its later involvement could be directly related to the appearance of positive symptoms. The relationship between positive psychotic symptoms and the hippocampus—especially the CA3 area—lies at the core of theoretical frameworks connecting memory and hallucinations [25, 27] and has been further corroborated by empirical evidence. Tamminga et al. proposed that hallucinations arise from the imbalance between the independent mechanisms of pattern separation and pattern completion, respectively, involved in distinguishing new sensory inputs that differ slightly from previously stored memories and in the retrieval of memories from fragmented sensory cues [27]. The CA3 area is responsible for both of these processes. If there is a DG hypofunction, which is heavily involved in pattern separation [79], then hyperactivity in CA3-driven pattern completion [80] leads to wrong associations and false memories, possibly resulting in hallucinations [27, 81]. In keeping with this theory, it has been demonstrated that FEP and chronic schizophrenia patients have a selective impairment in pattern separation with respect to healthy controls [82–84]. Subsequently, as shown in other studies, hippocampal hyperactivity can later lead to atrophy [28, 85]. Consistent with this, only those patients with Parkinson's disease experiencing hallucinations exhibited hippocampal atrophy [86]. Furthermore, 21% of patients with selective hippocampal stroke experienced transient hallucinations [87]. Hence, the connection between positive symptoms, especially hallucinations, and a decreased hippocampal volume becoming increasingly accepted in the literature.

Nevertheless, the quest to understand the relationship between hippocampal dysfunction and psychosis is yet to be completed, as we still do not know at what point of development it occurs. Our findings showed that several right-side hippocampal subfields atrophied over time starting from late adolescence in 22q11DS psy+ patients. Accordingly, a multisite study demonstrated the highest rate of subthreshold positive symptoms in patients with 22q11DS during adolescence [56], suggesting that hippocampal volume decreases occurred in a period that was sensitive to the emergence of psychotic symptoms.

Overall, in 22q11DS psy+ patients, atrophy started in the CA1 area and subsequently involved the DG, CA4 and CA2/3 subfields. Interestingly, a similar pattern of progression has been previously described in the early phases of schizophrenia, with hippocampal volumetric deficits spreading over time from CA1 to CA2/3 and DG [18]. Our results not only confirmed such a progression but also specifically associated CA3 volumetric loss with the presence of psychotic symptoms. Therefore, our findings add to the effort of defining the timeframe in which preclinical pathophysiological processes occur, leading to the onset of the first psychotic symptoms.

On the other hand, the left-side hippocampus group differences started from the age of 6 without divergent trajectories. We do not know whether these asymmetrical trajectories were due to inadequate sample size or depend on some functional hemispheric specialization. Hippocampal asymmetry, with a larger right side, has been demonstrated at every stage of healthy development in adults [88], children [89] and infants [90], as well as in patients with schizophrenia [91]. Likewise, in other studies,

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the right hippocampal volume had a different developmental trajectory from the left [67], increasing more quickly from childhood to adolescence [92]. Our findings of lateralized trajectories might, therefore, reflect a different speed of the pathophysiology of schizophrenia within the right hippocampus and left hippocampus. A captivating hypothesis is that the asymmetry of carotid and vertebral arteries reported in deletion carriers [93] and related to the abnormal development of the derivatives of the third and fourth branchial arches might partly explain our lateralized findings. However, future studies in larger samples are needed to test whether asymmetrical trajectories of hippocampal development are related to the risk of psychosis.

Lower hippocampal volume is associated with the presence rather than the degree of positive symptoms

We tested whether the severity of positive symptoms was correlated with the degree of hippocampal volume loss in each subfield. Although there is evidence for such a correlation in independent samples of patients with schizophrenia [74, 75], in our group of patients with 22q11DS, we did not find any significant result. Nonetheless, we demonstrated subfield-specific progressive involvement starting in late adolescence, suggesting that there is indeed a link between disease progression and hippocampal volume decrease.

This discrepancy might be explained by the fact that positive psychotic symptoms have an inherently fluctuating nature that does not necessarily parallel the general progression of the disease [94], especially in patients with 22q11DS [42, 95].

Hippocampal volume as a vulnerability factor for psychosis: hypotheses and perspectives

Considering our findings, it is worth noting that the volumes of most of the areas expected to have a role in psychosis, such as CA1, DG, CA4 and subiculum, were already lower in the entire 22q11DS group compared to the HC group. Therefore, we cannot ignore the fact that 22q11DS is per se a risk factor for the development of psychosis. Furthermore, 22q11DS psy+ patients had a smaller left-side hippocampus starting from the age of 6. Taking into account hallucinations instead of the SIPS score (Supplementary Information), allowed us to include more patients between the ages of 6 and 10, showing that patients with hallucinations had a smaller right-side hippocampus even during childhood. Taken together with the observation that these areas undergo a further decrease during late adolescence, it is conceivable that a smaller hippocampal volume at baseline could be a vulnerability factor for developing positive psychotic symptoms and hippocampal atrophy.

We, therefore, propose a framework that could explain our results in light of some recent findings. Increased hippocampal activity, either in cerebral blood flow [28] or glutamatergic tone [30, 80], has been shown to precede atrophy in psychotic patients and mouse models [28, 30, 96]. The most commonly accepted interpretation is that enhanced glutamatergic activity requires an increased blood supply and can lead to atrophy through excitotoxicity mechanisms [31]. Interestingly, a continuum of increased glutamate levels has been found from controls to psychotic 22q11DS patients using MRS [97], suggesting that premorbid 22q11DS patients might have an excitatory/inhibitory imbalance that worsens along with the progression of psychosis. We can speculate that reduced hippocampal volume at baseline could lead to compensatory mechanisms involving enhanced glutamatergic transmission. Then, environmental factors known to interfere with hippocampal physiology, such as stress [98] and neuroinflammation [99], may act as a second hit in some patients, resulting in an abnormally increased demand, which would, in turn, lead to psychotic symptoms and additional atrophy.

Further research is required to disentangle the relationship between hippocampal morphology and the excitatory/inhibitory imbalance in relevant subfields in patients with 22q11DS.

Limitations and conclusion

Several limitations need to be taken into consideration when interpreting our results. First, compared to HC, patients with 22q11DS had many psychiatric comorbidities. However, the aim of this analysis was to explore the overall effect of the 22q11.2 deletion on hippocampal development, irrespective of phenotypic manifestations. Second, 22q11DS psy+ were comparable to those without positive symptoms regarding each psychiatric comorbidity, except for having more than one psychiatric diagnosis and taking antipsychotic medications (Table 2). However, covarying for antipsychotic medications, which were shown in some studies to decrease hippocampal volume [100], did not affect any of our findings. Moreover, many other studies failed to demonstrate a direct relationship between hippocampal volume and antipsychotics [2, 10, 17, 18]. To rule out any interference of CHD and psychiatric comorbidities as anxiety and mood disorders, we added those variables as covariates, and there was still a strong effect of psychotic symptoms, both regarding the group effect and the interaction with age (Supplementary Table 6). Furthermore, we separately took into consideration anxiety and mood disorders and estimated the hippocampal developmental trajectories according to the diagnosis of each of these

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comorbidities. However, we did not find any evidence of an effect on hippocampal volume (Supplementary Table 7). Third, only 15 patients formally met the criteria for a diagnosis of schizophrenia; therefore, we lacked the power to predict the development of a full-blown disorder. Indeed, the psychosis literature would greatly benefit from longitudinal investigations of hippocampal development predicting the conversion to psychosis in patients with 22q11DS.

Although three different scanners were employed over time in data collection, the number of 22q11DS patients and HC acquired with each scanner was comparable (Tables 1 and 2), and the results were covaried according to the scanner model. Finally, the lack of data before the age of 6 and after 35 prevented us from obtaining a broader picture of hippocampal development, although adolescence is considered the most sensitive period for psychosis.

In summary, we demonstrated in a large sample of patients with 22q11DS a decreased hippocampal volume compared to HC, suggesting that this could be an anatomical trait of the syndrome. A progressive decrease in the volume of the right hippocampus starting from late adolescence was found in 22q11DS psy+ patients. With regard to hippocampal subfields, CA1 was the first affected area, while CA3 was the last, and its atrophy was exclusively correlated with positive symptoms.

As far as we are concerned, no study in the general population has ever longitudinally evaluated the occurrence of psychotic symptoms and hippocampal volume changes over such a broad timespan. Therefore, in light of our findings and considering that healthy relatives of schizophrenia patients carry hippocampal malformations [32–36], future studies should address whether a smaller or abnormal hippocampus is also present from childhood in non-syndromic subjects who will later develop schizophrenia.

Code availability

The code employed to model hippocampal developmental trajectories is available upon request.

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