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Dysmaturation Observed as Altered Hippocampal Functional Connectivity at Rest Is Associated With the Emergence of Positive Psychotic Symptoms in Patients With 22q11 Deletion Syndrome

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ABSTRACT

BACKGROUND: Hippocampal alterations are among the most replicated neuroimaging findings across the psychosis spectrum. Moreover, there is strong translational evidence that preserving the maturation of hippocampal networks in mice models prevents the progression of cognitive deficits. However, the developmental trajectory of hippocampal functional connectivity (HFC) and its contribution to psychosis is not well characterized in the human population. 22q11 deletion syndrome (22q11DS) offers a unique model for characterizing early neural correlates of schizophrenia.

METHODS: We acquired resting-state functional magnetic resonance imaging in 242 longitudinally repeated scans from 84 patients with 22q11DS (30 with moderate to severe positive psychotic symptoms) and 94 healthy control subjects in the age span of 6 to 32 years. We obtained bilateral hippocampus to whole-brain functional connectivity and employed a novel longitudinal multivariate approach by means of partial least squares correlation to evaluate the developmental trajectory of HFC across groups.

RESULTS: Relative to control subjects, patients with 22q11DS failed to increase HFC with frontal regions such as the dorsal part of the anterior cingulate cortex, prefrontal cortex, and supplementary motor area. Concurrently, carriers of the deletion had abnormally higher HFC with subcortical dopaminergic areas. Remarkably, this aberrant maturation of HFC was more prominent during midadolescence and was mainly driven by patients exhibiting subthreshold positive psychotic symptoms.

CONCLUSIONS: Our findings suggest a critical period of prefrontal cortex–hippocampal–striatal circuit dysmaturation, particularly during late adolescence, which in light of current translation evidence could be a target for short-term interventions to potentially achieve long-lasting rescue of circuit dysfunctions associated with psychosis.

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Schizophrenia is a severely disabling mental disorder for which the complexity of the underlying mechanisms is still largely unknown. Even though full-blown psychosis is typically diagnosed during early adulthood, the clinical course of the symptoms can be traced back to a subclinical state that has often already manifested during adolescence. Moreover, etiological factors such as genetic predisposition and environmental contributors may act even earlier, as suggested by subtle neurodevelopmental abnormalities during childhood (1,2). In fact, the psychotic phase of schizophrenia is now believed to be the final consequence of an atypical ongoing neural process during brain development (3). The notion of this neurodevelopmental mechanism suggests that aside from the type of treatment, early intervention is particularly important in improving treatment outcomes (4,5). Consequently, characterizing the developmental course of schizophrenia would be critical in identifying sensitive time windows for intervention. In this sense, neuroimaging studies could help to identify deviations in brain development that precede the emergence of clinical symptoms.

Among the neural biomarkers of schizophrenia, hippocampal (HIP) alterations are among the most replicated findings. Studies on patients with schizophrenia report HIP changes that converge with morphologic anomalies such as reduction in volume (6–9). Moreover, different techniques have provided evidence of HIP functional hyperactivation (10–12). Both functional and structural alterations in the hippocampus have been further attributed to psychosis by the presence of a

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dose–response relationship in patients who show attenuated psychotic symptoms (13). However, it is well established that psychosis is better described as a dysfunction of brain connectivity rather than isolated regional malfunctions (14,15). Correspondingly, disrupted structural connectivity between the hippocampus and cortical regions has been frequently proposed as a relevant marker in schizophrenia (16,17). Moreover, deficits in functional coordination between the hippocampus and various brain regions such as parahippocampal gyri, the medial prefrontal cortex (PFC), and (more largely) the default mode network have been documented (18–21). Similar but less severe alterations in functional connectivity have been reported in patients in the prodromal phase of the disease, specifically in regard to the PFC and anterior cingulate (21–23).

Despite this well-established role for the hippocampus, the developmental trajectory of this core biomarker in relation to the onset of symptoms is not well understood. Unquestionably, characterizing brain maturation during early premorbid stages is extremely challenging, partly due to the low incidence of psychosis in the general population. For that reason, the study of populations who are at a higher risk for developing psychosis could present a promising approach (24). Among these, 22q11 deletion syndrome (22q11DS), by presenting a 40% risk of progression into psychosis (25), provides a unique opportunity to investigate the earliest underlying neuropathologies of schizophrenia (26). In particular, recent evidence has shown that a developmental shrinkage of the hippocampus during adolescence is related to emergence of psychosis in this population (27). Moreover, aside from morphological alterations, studies on mice models of 22q11DS have shown that early HIP dysconnectivity may predict subsequent developmental deficits (28,29). Strikingly, both HIP dysconnectivity and subsequent functional deficits could be rescued through early treatment targeting a sensitive developmental time window during late adolescence of the mice models (28). Nevertheless, to date no study has longitudinally characterized the maturation of hippocampal functional connectivity (HFC) in individuals with 22q11DS, which is presumably relevant for identifying sensitive windows for intervention.

Given these findings, the goal of the current study was to characterize how maturation of HIP resting-state functional connectivity in patients with 22q11DS differs from that in the normal population using a multivariate approach. Furthermore, we sought to investigate whether abnormal HFC is associated with the emergence of psychosis. We hypothesized that in patients with 22q11DS, HFC with the prefrontal regions would be disrupted. We further expected that HIP dysconnectivity would emerge during adolescence and would be more severe in participants who later develop positive psychotic symptoms.

METHODS AND MATERIALS

Participants

A total of 84 participants with a diagnosis of 22q11DS (54.76% female, age span 8–32 years) and 94 healthy control subjects (HCs) (55.31% female, age span 6–32 years) underwent successive magnetic resonance imaging (MRI) scans. HCs were recruited from unaffected siblings of the patients or through an open call to the Geneva State School system in Switzerland, after which they were controlled for any history of psychopathology and developmental abnormalities and were matched for age, sex, average number of scans, and average spacing between visits. Participants with 22q11DS and their parents were invited to participate in the study only if they had received a confirmed genetic diagnosis of 22q11.2 deletion syndrome from a local genetics department. The presence of a 22q11.2 deletion was then confirmed using quantitative fluorescent polymerase chain reaction by the Department of Medical Genetics in Geneva. In total, 46.7% of assessments were accompanied by at least one other longitudinal assessment. A detailed summary in regard to the number of repetitive assessments is available in the Supplement.

In each visit, participants with 22q11DS underwent a comprehensive clinical assessment with an expert psychiatrist (author SE), including a semistructured clinical interview, to assess the presence of comorbid psychiatric conditions (30–32). In addition, the Structured Interview for Prodromal Syndromes (33) was administered to a subgroup of participants to assess the presence of attenuated symptoms of psychosis. Some participants were not assessed by the Structured Interview for Prodromal Syndromes owing to their young age (n = 4). In line with previous studies from our group (27,34,35), we used the Structured Interview for Prodromal Syndromes to constitute subgroups based on the participants' clinical characteristics. Patients were considered PPS(+) (positive psychotic symptoms; n = 30) if they scored equal to or higher than 3 in at least one visit on any of the subscales for positive psychotic symptoms (Unusual Thought Content, Suspiciousness, Grandiosity, Hallucinations, and Disorganized Communication) (36). The remaining participants were considered PPS(−). Participants' clinical characteristics are further listed in Table 1.

Written informed consent was obtained from all participants or their parents under protocols approved by the Swiss Ethical Committee (Commission Centrale d'Ethique de la Recherche, Geneva Canton). A summary of criteria for the exclusion of subjects from our initial scans is available in the Supplement.

Image Acquisition and Preprocessing

Structural and functional MRI data were acquired at the Centre d'Imagerie BioMédicale in Geneva on a Siemens Trio (n = 229) and a Siemens Prisma Fit (MAGNETOM Trio upgrade) (n = 13) 3T scanner (Siemens Corp., Erlangen, Germany). Structural image acquisition was conducted using a T1-weighted sequence with 192 slices. The volumetric resolution was $0.86 \times 0.86 \times 1.1$ mm^3 (repetition time = 2500 ms, echo time = 3 ms, field of view = 23.5 cm^2, flip angle = 8°, acquisition matrix = 256 × 256, slice thickness = 1.1 mm, phase encoding right > left, no fat suppression). Resting-state scans were performed while the participants were instructed to fixate on a white cross on the screen and stay awake. Functional MRI scans were obtained with a T2-weighted sequence (200 frames, acquisition matrix = 94 × 128, field of view = 96 × 128, voxel size = 1.84 × 1.84 × 3.2 mm^3, 38 axial slices, slice thickness = 3.2 mm, repetition time = 2400 ms, echo time = 30 ms, flip angle = 85°, phase encoding anterior > posterior, descending sequential ordering, GRAPPA [generalized

Table 1. Participant Characteristics

	PPS(+)	PPS(−)	HC	*p* Value of PPS(+) vs. PPS(−)	*p* Value of 22q11DS vs. HC
Number of Scans	45	68	124	NA	NA
Average Time Between Longitudinal Visits, Years, Mean (SD)[a]	3.98 (0.73)	4.12 (1.10)	4.04 (0.87)	.71	.98
Number of Subjects (Female/Male)	30 (15/15)	50 (28/22)	94 (52/42)	.60[b]	.93[b]
Age, Years, Mean (SD)[a]	18.24 (6.0)	18.63 (5.2)	17.01 (5.7)	.77	.20
IQ, Mean (SD)[a]	70.3 (13.7)	73.52 (14.0)	110.10 (14.4)	.32	<.001[c]
Framewise Displacement Before Scrubbing, Mean (SD)[a]	0.19 (0.06)	0.21 (0.07)	0.16 (0.07)	.13	<.001[c]
Framewise Displacement After Scrubbing, Mean (SD)[a]	0.16 (0.05)	0.17 (0.05)	0.14 (0.05)	.27	<.001[c]
	PPS(+), *n* (%)	PPS(−), *n* (%)	22q11DS, *n* (%)	HC, *n*	*p* Value of PPS(+) vs. PPS(−)
Anxiety Disorder[d]	14 (46.7%)	12 (24.0%)	27 (32.1%)	0	.036[c]
Attention-Deficit/Hyperactivity Disorder[d]	17 (56.7%)	16 (32.0%)	35 (41.7%)	0	.030[c]
Mood Disorder[d]	15 (40.5%)	8 (16.0%)	25 (29.8%)	0	.001[c]
Schizophrenia Spectrum Disorders[d]	10 (33.3%)	0	10 (11.9%)	0	NA
More Than One Psychiatric Comorbidity[d]	20 (66.7%)	18 (36.0%)	38 (45.2%)	0	.008[c]
Anticonvulsants[d]	1 (3.3%)	0	1 (1.2%)	0	NA
Antidepressants[d]	9 (30.0%)	1 (2.0%)	10 (11.9%)	0	<.001[c]
Neuroleptic[d]	11 (36.7%)	3 (6.0%)	15 (17.9%)	0	<.001[c]
Psychostimulant[d]	13 (43.3%)	12 (24.0%)	26 (30.9%)	0	.07
Anxiolytic[d]	6 (20.0%)	0	7 (8.3%)	0	NA

IQ measurement: Wechsler Intelligence Scale for Children-III (75) for children and Wechsler Adult Intelligence Scale-III (76) for adults. Presence of psychiatric disorders: Clinical interview with patients using the Diagnostic Interview for Children and Adolescents–Revised (30), the psychosis supplement from the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (31), and the Structured Clinical Interview for DSM-IV Axis I Disorders (32).

HC, healthy control subjects; NA, not available; PPS(+), with positive psychotic symptoms; PPS(−), without positive psychotic symptoms; 22q11DS, 22q11 deletion syndrome.

[a]Calculated first-level average within subject measurements, and then second level across all subjects.

[b]Significant at the level of $p < .05$ (χ^2 test).

[c]Significant at the level of $p < .05$ (*t* test).

[d]Positive if present at any of the repetitive assessments.

autocalibrating partially parallel acquisitions] acceleration mode with factor for parallel imaging = 2) for 8 minutes (37).

Preprocessing of the functional images was conducted using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) and functions of the DPARSF (38) and IBASPM (39) toolboxes. An explanation of the resting-state functional MRI preprocessing pipeline is provided in the Supplement.

HIP Connectivity

For HIP connectivity analysis, a mask of the bilateral hippocampus as the region of interest based on the AAL-90 (Automated Anatomical Labeling 90) (36,37) atlas (40) was selected and spatially transformed into the individual subject space through the study-specific DARTEL template (41). (Separate analyses for the left and right HIP mask generated similar results and are available in the Supplement.) Seed functional connectivity maps were obtained by computing the Pearson correlation coefficient for each voxel's time course with the average time course inside the region of interest. Voxelwise seed functional connectivity maps were then warped into DARTEL space and further into the Montreal Neurological Institute space (42).

Partial Least Squares

To investigate the neurodevelopmental trajectory of HIP connectivity patterns, we applied the partial least squares correlation (PLS-C) (43,44) using the myPLS toolbox (45), for which the implementation is publicly available (https://github.com/danizoeller/myPLS). In short, a cross-covariance matrix (*R*) is computed between the HIP connectivity maps per subject (*X*) and a set of design variables (*Y*) that are chosen to encode diagnosis, longitudinal and cross-sectional age, and their interactions. Before entering the maps into PLS-C, sex and motion (average framewise displacement after scrubbing) were regressed out voxelwise. For the design variables, we start by including a binary variable of diagnosis, which is (depending on the analysis) either HCs versus patients with 22q11DS or PPS(+) versus PPS(−). Given the presence of multiple time points per subject, and to correctly capture the within- and between-subject effect of age, we set up two age variables. First, mean age assigns the average age of that subject across

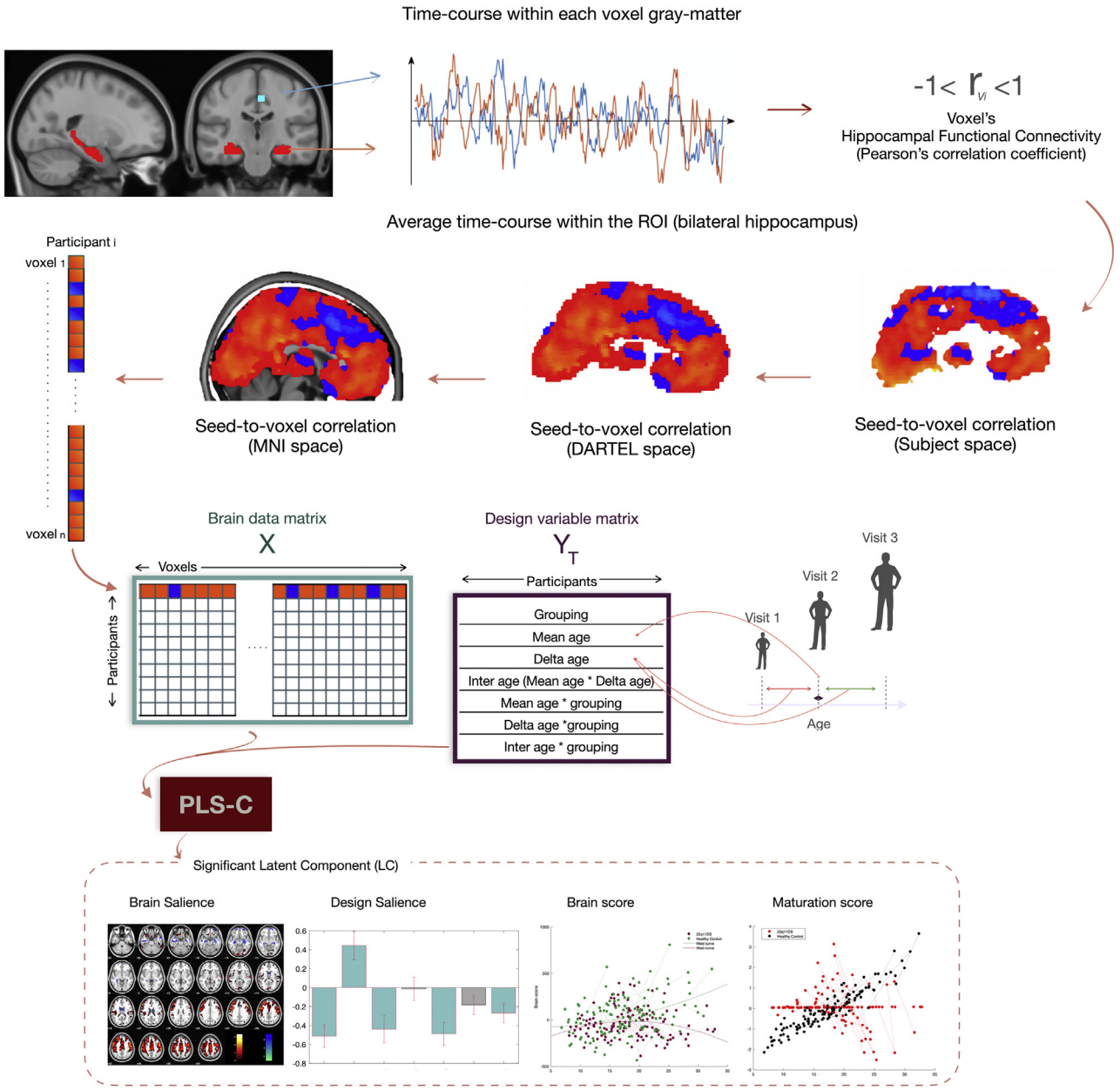

Figure 1. Analysis pipeline and longitudinal partial least squares correlation (PLS-C) analysis. LC, latent component; MNI, Montreal Neurological Institute; ROI, region of interest; 22q11DS, 22q11 deletion syndrome.

all visits for each time point. Next, delta age corresponds to the difference between the actual age of a subject at a time point and the subject's mean age. It is worth noting that, by construction, mean age and delta age are orthogonalized and can be interpreted as the cross-sectional and longitudinal effect of age, respectively. We then defined inter age as the interaction between mean age and delta age, which enables the capture of concave or convex (i.e., U-shaped) neurodevelopmental trajectories. To allow the model to capture the difference of the developmental trajectories within the two groups, we also provided the interaction of the diagnosis variable with each of the three age-related variables (35), adding a further three variables to the design matrix. Finally, a total of seven variables were included and were *z* scored across all subjects. The matrix R is then computed as $R = Y^T X$ and subjected to the singular value decomposition ($R = USV^T$)[1], which in turn leads to latent components (LCs) (Figure 1).

To test the significance of the correlation explained, we applied permutation testing with 1000 permutations and

[1] Y^T (the transposed matrix of Y) multiplied by X equals R; U is the matrix containing left singular vectors; S is the matrix containing singular values; and V is the matrix containing right singular vectors.

applied a Bonferroni correction for multiple comparisons while testing for the seven components. The LC was considered significant if the *p* value was less than .007.

For those LCs found to be significant, the stability of the results was tested using a bootstrap of 500 random samples with replacement. Given the longitudinal construction of our data set, we made the random selection of samples across subjects and not scans. In this way, all intrasubject dependencies were respected across the bootstrap samples. The bootstrap score was calculated as the mean of distribution of all brain saliences for each voxel divided by their standard deviation. This in turn provides a measure of stability of a particular voxel in its contribution to the detected correlation. In this study's brain pattern visualization, bootstrap ratio scores were thresholded at an absolute value greater than 2.3, which corresponds to a 99% confidence interval not crossing zero and indicates a stable contribution from this variable to the LC (44).

Maturation Pattern

To be able to more easily interpret the age relationship that was revealed in a latent variable, we built the scatterplot between actual age and the maturation score that contains only the age-related contributions of the behavioral score, as shown in Figure 2. This offers a better insight into the effect of aging alone (disregarding the group difference) on HFC maturation captured by PLS. In participants with 22q11DS, the failure to normally develop HFC is already present at the beginning of our age span (Figure 2A). However, the drop in HFC maturation is mostly observed as a longitudinal change regarding baseline connectivity in patients. Furthermore, the longitudinal dysmaturation could be detected as early as the beginning of adolescence (before 15 years of age).

Furthermore, to have a measure of how well each subject's data are explained by the correlation of brain values observed in a certain LC, we compute brain scores (*Lx*) as the projection of the original brain value for all subjects (*X*) in the brain salience (*V*), thereby calculating ($Lx = XV$). We fitted a polynomial curve using the linear least squares to visualize the relationship of brain scores with age and age^2 (as indicated by the effect of inter age) in Figures 3C and 4C.

To offer complementary insight into the original baseline HFC values, Figure 5 shows regions that functionally connect positively (red) or negatively (blue) with the hippocampus in the 4 separate groups: HCs and patients younger than 12 years (21 HCs and 16 patients with 22q11DS) and HCs and patients older than 22 years (15 HCs and 17 patients with 22q11DS). These age bins were chosen as a post hoc analysis to the PLS-C because we observed that the age effect captured by PLS-C was more dynamic between 15 and 20 years of age (see maturation patterns in Figure 2).

RESULTS

Comparing Patients With 22q11DS Against HCs

PLS-C analysis on longitudinal data of seed-to-voxel HFC resulted in one significant component (LCs; $p < .001$) (Figure 3), which captured both overall differences in HFC across cohorts, as revealed by a stable diagnosis effect, and

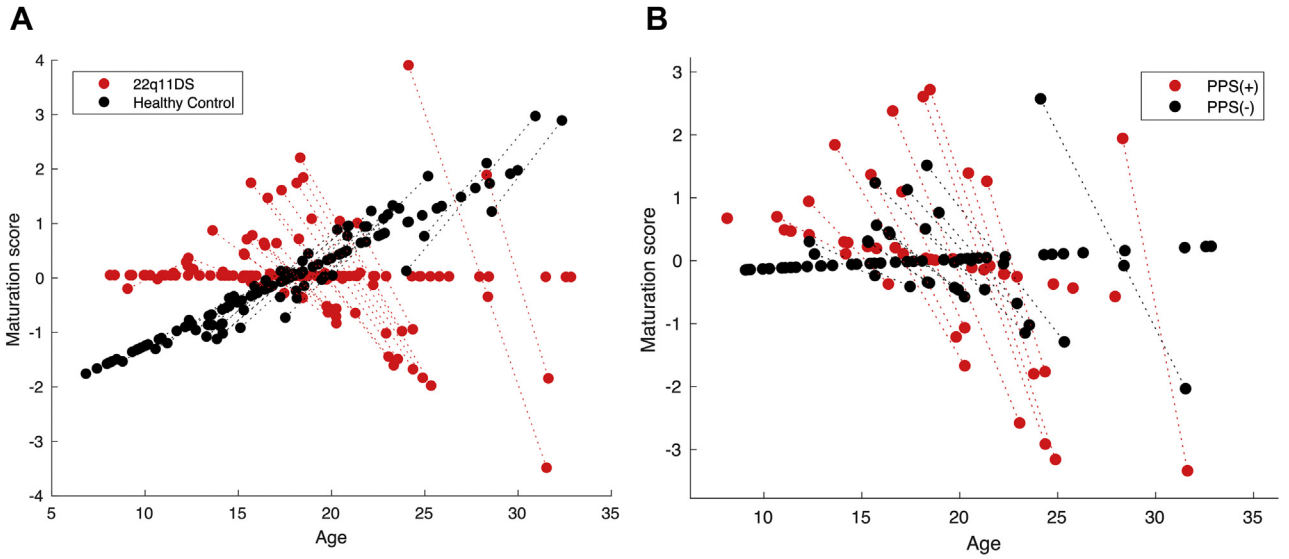

Figure 2. Maturation patterns. Maturation scores were calculated as the projection of the 6 age-related design saliences (mean age, delta age, and quad age and their interaction with the grouping variable) into the respective behavioral variable of each subject and plotted against actual age. Therefore, this pattern reveals the effect of aging captured by the partial least squares correlation. **(A)** Comparing patients with 22q11 deletion syndrome (22q11DS) with healthy control subjects reveals that the age score increases with age in healthy control subjects but longitudinally decreases in patients. The cross-sectional effect of age is already present at the beginning of the studied age span (6 years). However, the abnormal longitudinal decrease in age scores of patients starts as early as 15 years. **(B)** Comparing patients with and without positive psychotic symptoms [PPS(+) vs. PPS(−)] revealed that the longitudinal drop in age scores becomes more severe in PPS(+) patients during midadolescence.

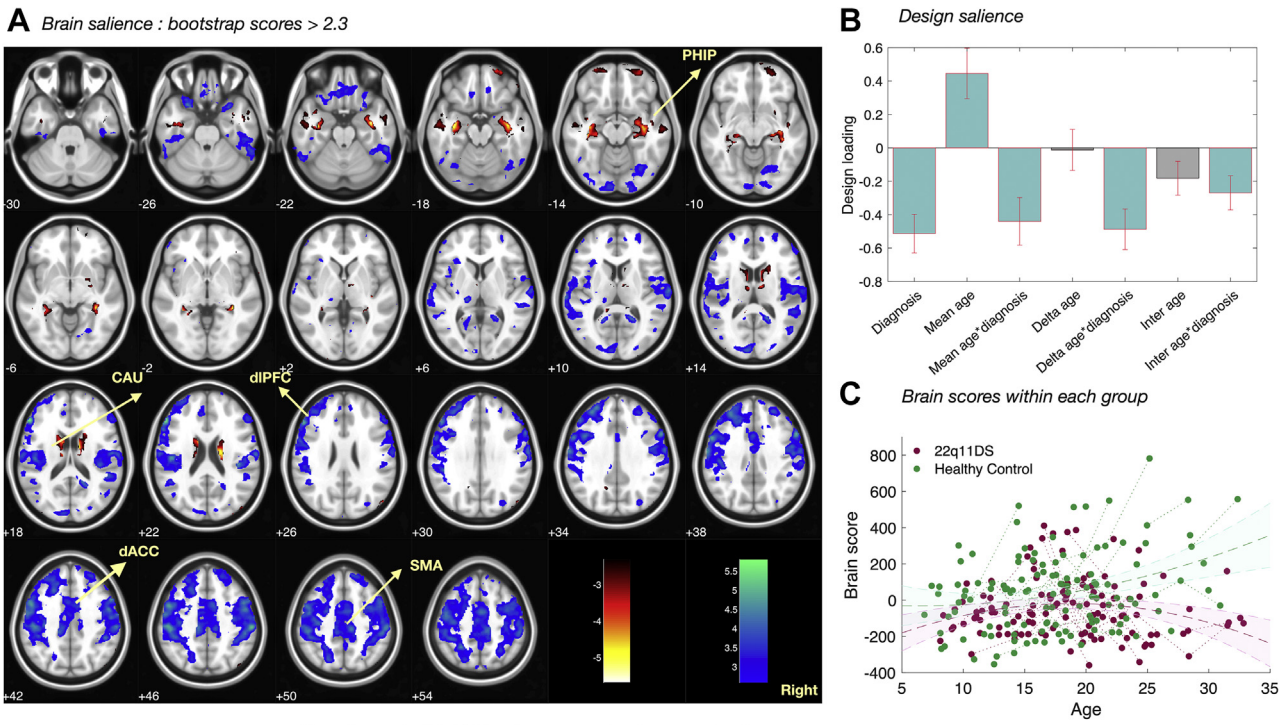

Figure 3. Comparing maturation of hippocampal functional connectivity in patients with 22q11 deletion syndrome (22q11DS) and healthy controls subjects. The one significant latent component resulted from the partial least squares correlation analysis. **(A)** The pattern of brain saliences can be interpreted as areas of lower and developmental failure to increase hippocampal connectivity (blue) and higher and developmental failure to decrease hippocampal connectivity (red) in patients with 22q11DS. **(B)** Design salience of the latent component reveals the negative effect of diagnosis as well as a negative effect of age–diagnosis interaction. **(C)** The distribution of brain scores across age in each group provides an alternative view on those partial least squares correlation results: Brain scores are lower in patients with 22q11DS (negative diagnosis effect). In addition, brain scores are less affected by aging (negative interaction effect) in patients, which points toward a dysmaturation. Fitted line and 95% confidence interval are plotted to visualize the age and diagnosis interaction effect captured by partial least squares correlation in the bar plot in **(B)**. CAU, caudate nucleus; dACC, dorsal part of anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; PHIP, parahippocampal cortex; SMA, supplementary motor area.

differences in HFC maturation, as revealed by a stable age by diagnosis interaction.

Figure 3 shows the brain and behavioral saliences for the significant component. The age-related loadings in Figure 3B are reflected as the aberrant developmental trajectory visualized in Figure 3C as a fitted curve to the brain scores. This trajectory shows an abnormal maturation for HFC that is mostly detected by the effect of age (stable age loadings). Moreover, the prominent deviation from a normal trajectory is particularly present during midadolescence (stable inter age × diagnosis loading).

Our multivariate approach revealed a brain pattern that was characterized by two sets of regions showing opposite developmental alterations of HFC. Specifically, a first set of regions, displayed in blue in Figure 3A, presented a developmental failure to increase HFC in 22q11DS. Such developmental failure affected clusters in the dorsal part of the anterior cingulate cortex (dACC) as well as the precentral, postcentral, and supplementary motor areas. As a consequence of such developmental alteration, by adulthood HFC at the level of the dACC and supplementary motor cortex had an opposite direction across the two samples (positive in HCs and negative in patients with 22q11DS), as indicated by the presence of the blue clusters in Figure 5D that are, however, absent in Figure 5B. Thus, it can be interpreted that patients (unlike HCs) fail to develop a positive HFC with dACC and supplementary motor areas, and the HFC remains negative within these regions. A second set of brain regions, displayed in red in Figure 3A, showed an opposite failure to decrease HFC in 22q11DS and included the bilateral caudate nucleus and parahippocampal gyri.

Comparing PPS(+) Against PPS(−)

On the second PLS-C analysis, the significant component ($p < .001$) (Figure 4) revealed regions for which the HFC strongly and longitudinally is altered with age in PPS(+) patients but not as strongly in PPS(−) patients (Figure 4B). As visualized by the diverging developmental trajectory in Figure 4C, the major difference in HFC dysmaturation emerges only during midadolescence.

In PPS(+) patients, clusters in the dACC and dorsal PFC became more sharply dysconnected from the hippocampus as well as regions in the pre- and postcentral and supplementary motor areas, middle orbitofrontal gyrus, and clusters in the posterior inferior temporal gyrus. The regions with steeper

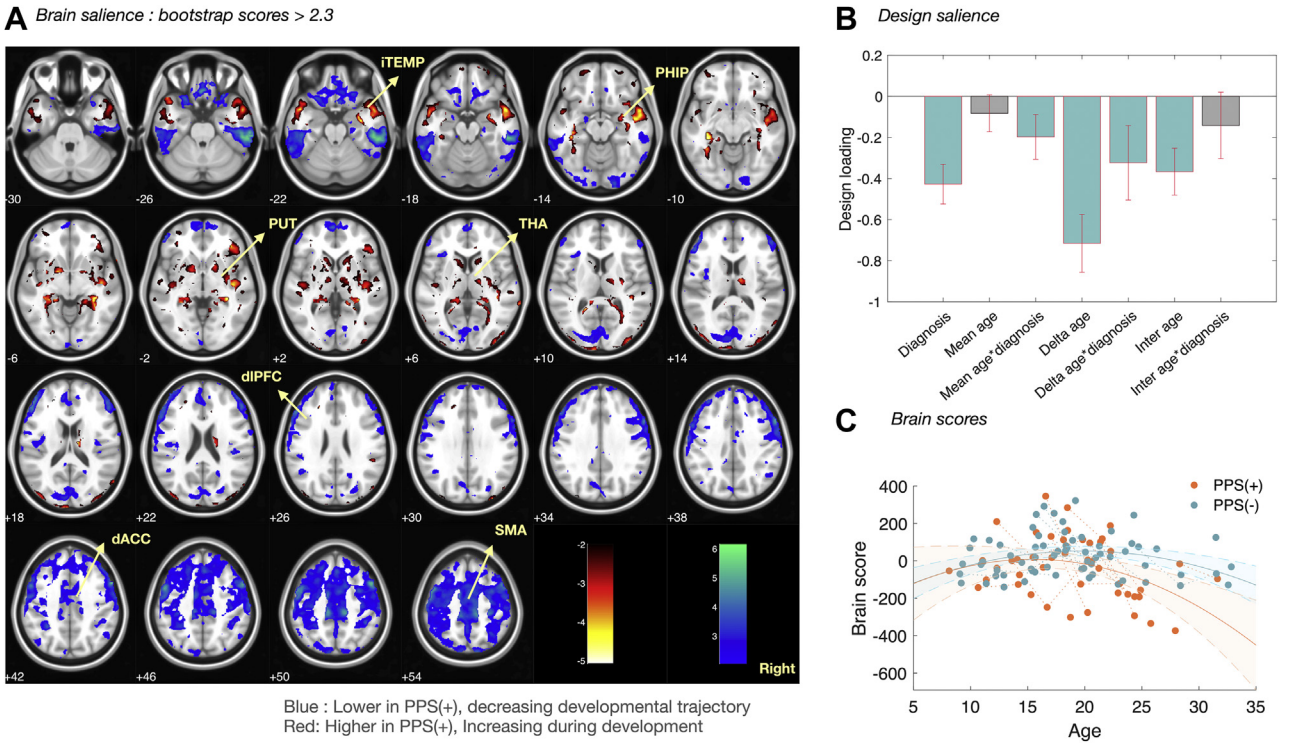

Figure 4. Comparing maturation of hippocampal functional connectivity (HFC) in patients with and without mild to moderate positive psychotic symptoms [PPS(+) and PPS(–), respectively]. **(A)** The pattern of brain salience shows areas with more severe decrease of HFC (blue) and increase of HFC (red) over the age span. **(B)** Design salience of the latent component reveals the negative effect of group as well as a negative effect of age–group interaction. Remarkably, the most prominent effect of age is captured within the longitudinal assessments (negative delta age and inter age effect). **(C)** The distribution of brain scores across age in each group shows that HFC maturation in PPS(+) patients deviates further from that in PPS(–) patients during adolescence. Fitted line and 95% confidence interval are plotted to visualize the age and diagnosis interaction effect captured by partial least squares correlation in the bar plot in **(B)**. dACC, dorsal part of anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; iTEMP, inferior temporal gyrus; PHIP, parahippocampal cortex; PUT, putamen; SMA, supplementary motor area; THA, thalamus.

developmental increases of HFC in symptomatic patients include the temporal pole, bilateral dorsal insula, and clusters in the anterior thalamus and bilateral putamen. This would suggest that PPS(+) patients drive the failure to decrease in HIP–striatum connectivity as well as the longitudinal decrease of HFC observed in PFC/dACC and supplementary motor area that is observed in the first diagnosis component (Figure 3A).

DISCUSSION

In this study, we used a multivariate longitudinal analysis to investigate hippocampus to whole-brain resting-state functional connectivity in a large cohort of patients with 22q11DS. We provide evidence on the aberrant development of HFC in individuals with 22q11DS and its contribution to psychosis pathophysiology.

Our results in the 22q11DS population revealed a pattern of HFC dysmaturation that was further aggravated during midadolescence. In particular, HFC dysmaturation was characterized by a failure to increase HFC with the PFC and dACC. To the extent of our knowledge, only one previous cross-sectional study has investigated whole-brain resting-state HIP connectivity in patients with 22q11DS and reported (in line with our findings) a disrupted HFC with sensory-motor regions (46). Moreover, our findings further confirm the state of dACC/PFC negative functional connectivity with the hippocampus, which was observed in a recent study of dynamic functional connectivity with a partially overlapping sample (47). Developmentally, it is established that functional connectivity between the PFC and hippocampus consistently increases with age (48). The behavioral aspect of HIP–PFC/dACC maturation further reflects the gain of emotional regulation and cognitive development observed during adolescence (48–50). Therefore, cognitive and emotional deficits observed in 22q11DS could be, in part, attributed to the dysmaturation of this circuit.

In addition, we show that HIP–PFC/dACC developmental dysmaturation is driven mostly by patients at higher risk for emergence of psychosis. As such, PPS(+) patients experience a more steep longitudinal drop in their baseline HIP–PFC connectivity. In line with our findings, abnormal ACC resting-state connectivity in patients with 22q11DS has been previously implicated as one of the main discriminative patterns in the presence of psychotic symptoms (35,51). Moreover, previous research has already suggested aberrant HIP connectivity with PFC in schizophrenia and similarly in nonsyndromic individuals at a higher risk for psychosis (21,52–56). In particular, our longitudinal approach demonstrated that deficits in

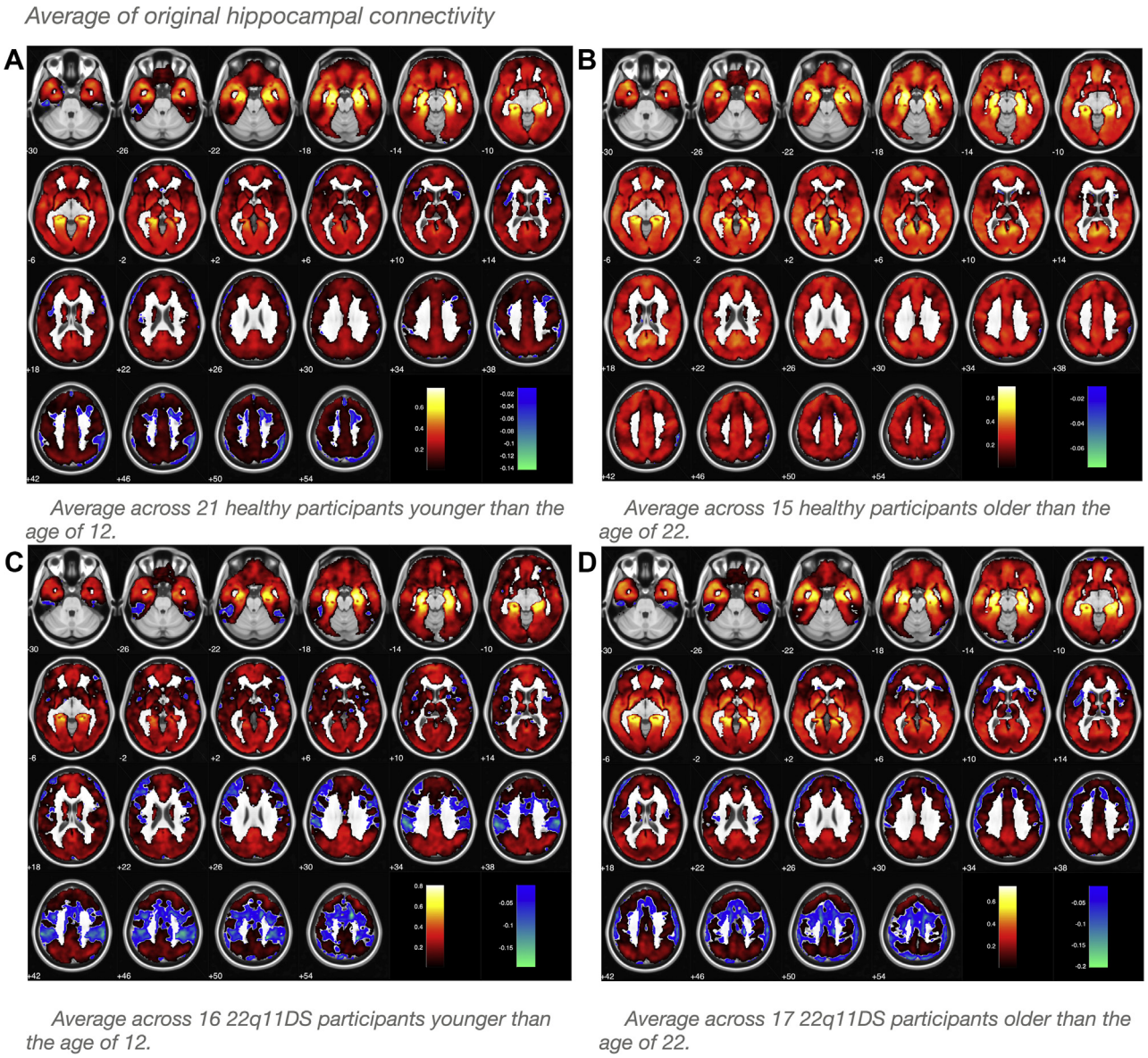

Figure 5. Averages of original hippocampal connectivity values. **(A)** Average across 21 healthy control subjects younger than 12 years. **(B)** Average across 15 healthy control subjects older than 22 years. **(C)** Average across 16 patients with 22q11 deletion syndrome younger than 12 years. **(D)** Average across 17 patients with 22q11 deletion syndrome older than 22 years.

HIP–PFC connectivity in PPS(+) patients emerge from a developmental drop during adolescence, which in turn is known as a critical period for the emergence of subthreshold psychotic symptoms both in patients with 22q11DS and in the general population (57).

The association between the HIP–PFC dysconnectivity and positive psychotic symptoms has been previously discussed in patients with schizophrenia in a framework of reduced top-down control over the hippocampus (18,23,58). Mainly, the deficit in functional coordination of HIP–PFC is suggested to be directed by insufficient fast-spiking parvalbumin (PV) GABAergic (gamma-aminobutyric acidergic) interneurons. The consequent decrease in GABAergic signaling has been accounted for overactivation of the hippocampus (59–62), which in turn has been largely associated with the presence of positive psychotic symptoms (63–66). Moreover, HIP hyperactivity has been shown to precede the HIP atrophy that is well documented in psychosis (13,67). Similarly, a recent investigation on a partially overlapping sample with the current study revealed a HIP volumetric decline during adolescence in PPS(+) patients (27). Of note, morphological deficits occurred at a later age compared with the HIP dysconnectivity detected in our study. Hence, HIP connectivity dysmaturation could potentially constitute an early biomarker of psychosis, predisposing to subsequent deleterious neurodevelopmental and clinical outcomes.

Remarkably, the multivariate nature of this study allowed us to reveal a HIP hyperconnectivity to subcortical dopaminergic regions that is present alongside the hypoconnectivity to the PFC. Notably, it has been suggested that PFC interneuron dysmaturation during adolescence could be directed by aberrant dopaminergic signaling (68). Here we show that patients with 22q11DS fail to decrease functional connectivity between the hippocampus and clusters in the dorsal striatum, which is further enforced toward adolescence. Once again, this developmental pattern appeared to be driven by PPS(+) patients, who displayed a steeper developmental increase of baseline HFC with the dorsal striatum compared with PPS(−) patients. Indeed, a major hypothesis regarding schizophrenia pathophysiology revolves around excess subcortical dopamine united with deficits in cortical dopamine signaling. It has been further hypothesized that the hippocampus may drive dopamine dysregulation in psychosis (69). In support of this hypothesis, it has been shown that the reduction in HIP PV expression and the consequent HIP hyperactivity could drive an overactivation in the ventral tegmental area (VTA) (10). Because midbrain regions are not included in our analysis, we do not know whether the same developmental pattern of HIP–VTA could be detected. However, the dorsal striatum is well connected to the midbrain (70), and HIP–VTA hyperconnectivity has been reported in the 22q11DS population (71). Therefore, our results regarding the co-occurrence of HIP-PFC dysconnectivity, on the one side, and HIP–striatal hyperconnectivity, on the other side, further confirm the hippocampus as a critical hub in this aberrant network (72).

One unique advantage of studying patients with 22q11DS is the availability of an exact translational model for the disorder (73). Undeniably, animal models are essential in shedding light on the underlying circuit dysfunction and in developing effective treatment strategies (3). Aptly, recent findings in mice models for 22q11DS point toward the importance of the hippocampus (28,29). The ventral hippocampus is accordingly the first region expressing PV interneuron hypoexcitability in the mouse brain, which further progresses to a state of brainwide PV recruitment deficit. Furthermore, both the ventral hippocampus and medial PFC become responsive to treatment during late adolescence. Remarkably, short-term administration of a D2R antagonist during a critical period at the end of adolescence resulted in long-term rescue of PV neuron recruitment that was dependent on HIP–PFC circuitry. The rescue of HIP–PFC PV neuron maturation was associated with long-lasting prevention of chronic cognitive and behavioral deficits in adult mice. Overall, our evidence fits particularly well with this translational evidence. Here we found a comparable pattern of HFC developmental trajectory, suggesting a matching critical role for HIP–PFC connectivity during adolescence. In addition, we show a concurrent increased HIP–caudate connectivity that has been previously linked to an increase in HIP D2R availability (74). Therefore, our findings regarding the surge of HIP–caudate connectivity during early adolescence could partly explain the window of D2R antagonist sensitivity during adolescence (28). Consequently, our findings could be fitted into the framework of a positive feedback loop, where an excess in subcortical dopamine is driven by HIP overdrive, which in turn is caused by HIP–PFC dysconnectivity. Our longitudinal approach allowed us to observe a critical period of PFC–HIP–striatal circuit dysmaturation during late adolescence. In light of translational findings, our results suggest that late adolescence might also represent a window of opportunity where short-term interventions could potentially achieve long-lasting rescue of circuit dysfunction associated with psychosis.

Considerations and Further Perspectives

Our results must be reflected upon within the framework of several methodological considerations. While the multivariate approach allowed us to detect significant patterns of developmental alterations, the pattern should be interpreted only as a whole and allows only limited conclusions about individual regions independent from the rest of the brain. Our longitudinal multivariate approach allowed us to assess developmental brain alterations alongside alterations within diagnostic groups; however, the interpretation of brain correlation with multiple diagnostic and age-related variables is challenging in itself. We made a particular effort to overcome this challenge by creating maturation scores and visualizing developmental trajectories.

Furthermore, within-scanner motion was significantly higher in patients with 22q11DS but did not differ within the psychopathology groups. Therefore, we regressed out motion as a nuisance variable from the connectivity matrix. Moreover, post hoc analysis revealed no association between movement and brain scores. A more detailed investigation regarding motion analysis and possible confounding factors is available in the Supplement.

The PPS(+) patients inevitably had more frequent psychological comorbidities and were using medication to a higher extent when compared with the PPS(–) patients (Table 1). Future extensive studies with bigger sample sizes are needed to investigate the role of each class of medication in HFC aberrant maturation. A more detailed investigation regarding the effect of medication and psychopathology is available in the Supplement.

Lastly, unaffected siblings were not systematically screened to confirm that they are not deletion carriers. However, participants with prematurity or a history of neurologic, developmental, or psychiatric difficulties were excluded, reducing the chance of including deletion carriers in the control sample.

In short, we demonstrate that patients with 22q11DS present an atypical trajectory of HFC. Here we observed that HFC dysmaturation was already partially present in patients with 22q11DS at 6 years of age, which may hint toward an earlier hit before the scope of our age span. Characterizing these earlier stages of HFC longitudinal maturation could be addressed in future studies investigating younger age groups. Notably, despite an early deficit, HFC dysmaturation longitudinally progressed during adolescence. For this reason, the diverging trajectory contributing to emergence of positive psychotic symptoms emerges during adolescence. In light of translational findings, future studies should elaborate whether this biomarker is indeed a potential treatment target for preventive interventions for psychosis.

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ARTICLE INFORMATION

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