Developmental trajectories of cortical thickness in relation to schizotypy during adolescence

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Abstract:

Investigating potential grey matter differences in adolescents presenting higher levels of schizotypy personality traits could bring further insights into the development of schizophrenia spectrum disorders. Research has yet to examine the morphological correlates of schizotypy features during adolescence prospectively, and no information is available on the developmental trajectories from adolescence to adulthood. We employed mixed model regression analysis to investigate developmental trajectories of cortical thickness (CT) in relation to schizotypy dimensions in a cohort of 109 adolescents from the general population for whom MRI-scans were acquired over a five year period, culminating in a total of 271 scans. Structural data were processed with FreeSurfer software, statistical analyses were conducted using mixed regression models following a ROI-based approach, and schizotypy was assessed with the Schizotypal Personality Questionnaire (SPQ). Accelerated thinning, was observed in the posterior cingulate cortex in relation to high levels of positive schizotypy, whereas high levels of disorganized schizotypy were associated with a similar trajectory pattern in the anterior cingulate cortex. The developmental course of CT in the prefrontal, occipital and cingulate cortices differed between adolescents expressing higher versus lower levels of negative schizotypy. Participants reporting high scores on all schizotypy dimensions were associated with differential trajectories of CT in posterior cingulate cortex and occipital cortex. Consistently with prospective developmental studies of clinical risk conversion, the negative

schizotypy dimension appears to constitute the most informative dimension for psychosis-related psychopathology, as its cerebral correlates in adolescents most closely overlap with results found in clinical high-risk for psychosis studies.

Introduction

The schizotypy construct encompasses genetic, biochemical, neurocognitive, phenotypic and behavioral characteristics that confer a latent vulnerability to develop psychotic disorders[1]. It connects with schizophrenia spectrum and other psychotic disorders at the level of factorial analyses in samples expressing non-clinical to clinical symptoms, yielding three factors: a positive factor (delusions and unusual perceptual experiences), a negative factor (social and physical anhedonia), and a disorganization factor (odd speech and behaviors). Individuals who report higher levels on psychometric schizotypy indeed express subtle emotional, behavioral, neurocognitive, psychophysiological and social impairments similar to patients with schizophrenia or schizotypal disorder[2,3,4]. Perhaps most significantly, from a prospective standpoint, longitudinal studies illustrate how schizotypy significantly predicts the risk for conversion to psychosis, in high risk for psychosis samples, familial risk samples, and personality disorder samples, but also in the general population samples[2]. As such, when reviewing 6 longitudinal studies including 7282 participants from the general population, 207 of them converted to psychosis (2.8%)[2]. Schizotypy thus constitutes a relevant developmental predictive factor when looking at clinical high-risk[5] of psychosis. Yet to date, little attention has been given to the neural underpinnings of schizotypy during adolescence, which represents a critical period for brain maturation[6], and a key period for clinical high-risk preceding first onset of psychosis[7].

From such a neurodevelopmental point of view, accumulated evidence in at-risk subjects who go on to develop psychotic disorders suggests atypical brain morphology[8] and atypical patterns of cerebral maturation[9]. A study following clinical high risk (CHR) individuals observed a steeper rate of thinning in medial and lateral prefrontal regions for converters in comparison to non-converters[10]. In another study, young CHR converters exhibited smaller surface area in rostral anterior cingulate, prefrontal regions and parahippocampal gyrus when compared to non-converters and remitters[11]. An additional study on CHR found that those who converted to psychosis exhibited less GM volume in the left para hippocampal cortex than those who did not convert[12]. Following the spectrum, it is also of interest to integrate cross-sectional

results obtained in cohorts of patients with first episode psychosis (FEP)[13,14]: CT alterations are localized in frontal[14] and temporal areas[15,16] . When considering patients with schizotypal personality disorders (SPD), a review identified structural brain abnormalities in superior temporal gyrus, para hippocampus, and thalamus[15,17]. Finally, at the clinical endpoint of the continuum, neuroimaging studies report brain structure abnormalities in schizophrenia diagnosed individuals, including grey matter (GM) volume reductions across the cortex, hippocampus and amygdala[18,10]. Altogether, these studies point to the progression of morphological brain alterations along the continuum of psychosis. However, little is known concerning the common cerebral endophenotypes between adolescent schizotypy and CHR, siblings as well as clinical samples.

To date, researchers studying schizotypy in the general population have contributed slightly more than a handful of studies of brain morphology in association to total or dimensional scores on schizotypy measures, yielding a set of disparate results[17,19–25]. The studies focusing on adult populations report that adults who score higher either on the SPQ total score[19] or on each dimension[20] , typically show less GM volume and CT in the frontal and temporal lobes, as well as anterior cingulum and insula[22,23]. In contrast, two studies report that high scorers on positive schizotypy present greater GM volumes in posterior cingulate cortex and precuneus[24,25]. Only two cross-sectional studies examined schizotypy during adolescence. The first study[26] included typically developing youths with high schizotypy (n=35) from 16 to 23 years old, who were found to display lower GM density around the region of the insula and dorsolateral PF gyrus. In the second study[21] involving youths (n=28) from 6 to 17 years of age, the positive schizotypy dimension was negatively associated with GM density in temporal and caudate volumes. While interesting, these studies were potentially underpowered, and none of them made use of longitudinal, multiple time points for each subject.

The current prospective study provides the first examination of the developmental trajectories between psychopathological traits of schizotypy during adolescence and cerebral endophenotypes in a longitudinal fashion. We propose a longitudinal mixed regression models approach, including data from 109 adolescents with one to five time points of visits. They will first be clustered into high and low scorers on each individual schizotypy dimension. Secondly, they will be defined by their schizotypy profiles, representing the combined levels of the three dimensions. The present study carries the potential to inform whether alterations in cerebral morphology found in CHR and/or siblings samples can also be observed in relation to schizotypy during adolescence.

We hypothesize that CT maturation patterns of individuals expressing high schizotypal features would relate to those found in community youths expressing high schizotypy (PFC, temporal and caudate regions). We anticipate that part of these patterns may reflect underlying pathogenesis, as seen in the initial stages of risk for psychosis. Therefore, we expect developmental differences in brain regions sharing commonalities with CHR converters (such as lateral and medial prefrontal, rostral anterior cingulate and/or para hippocampal regions), which would convey the common basis of risk for psychosis between adolescent schizotypy and CHR converters. The value of such research question is to find the earliest cerebral signatures of psychotic pathogenesis.

Methods

Participants

The study included a sample of 109 typically developing (TD) participants (60 males, 49 females). TD were recruited in the community and screened for the absence of acute psychotic phase, and estimated intellectual functioning on the Block Design and Vocabulary subtests below 1 std.dev of the developmental norm (based on the Cubes and vocabulary subtests of the Weschler Scales of Intelligence for children (WISC-IV) or for participants older than 18 y.o, the Wechsler Adult Intelligence Scale (WAIS-IV) detailed in the *supplementary material*). From the original sample of 123, 14 adolescents were excluded; 2 of them because they did not have a measure of vocabulary subtest, 7 because they suffered from diagnosed anxiety disorders and depression, 4 because they were diagnosed with ADHD and 1 presented schizoaffective disorder (see *supplementary material* for more details). All participants were French-native speakers, community adolescents and young adults with normal or corrected to normal vision. Recruitment was done by word of mouth and through advertisement in youth community centers around the Canton of Geneva. At the first visit the mean age was 15,98 (SD = 1,83), ranging from 12 to 20 years old (y.o). Individuals were enrolled in this longitudinal study and were assessed at multiple time points within a five years interval. Number of assessments varied between participants: a total of 271 scans was acquired comprising 27 individuals with one scan, 26 with two, 32 with three and 24 with four scans (see Figure1 and Table1). Participants received a financial compensation, and written consent was obtained from themselves or their parents (if they were under 18), under protocols approved by the local

ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux Universitaires de Genève).

Psychological Measures

We assessed adaptive behaviors using Adult Self Report and Youth Self Report as a control measure for internalizing and externalizing. Schizotypal personality traits were evaluated with the SPQ, which define 3 dimensions (positive, negative and disorganized. Refer to *supplementary material* for details on these measures.

Partition of Participants in Groups: Single dimensions analyses

To assess the potential influence of each single dimension of schizotypy on CT development we created groups of participant based on their SPQ score at first time point for each dimension (i.e., positive, negative, and disorganized) separately using optimal k-means clustering for univariate data implemented in R (*see supplementary material for more details*). The division yielded two subgroups for each dimension: high positive scorers (HPS) and low positive scorers (LPS); high negative scorers (HNS) and low negative scorers (LNS); high disorganized scorers (HDS) and low disorganized scorers (LDS).

Partition of Participants in Groups: Overall combined score analyses

For the subsequent analysis, we further analyzed the combined scores on the three SPQ dimensions. Using a double procedure combining K-means and Hierarchical agglomerative (Ward's method) clustering in R, partitioning of participants resulted into three clusters based on their SPQ scores in all dimensions at first time point to reflect their profiles on the three dimensions taken together. Among the three resulting clusters, one represented participants scoring high in all three dimensions classified as high schizotypy profiles (HS). The second cluster retained participants scoring intermediate in all three dimensions, referred to as intermediate schizotypy profiles (IS). The third cluster included participants scoring low in all three dimensions, the low schizotypy profiles (LS) (*see supplementary material for cluster analysis details*).

MRI Acquisition and Pre-processing

Acquisition and preprocessing methods were identical to both analyses.

Acquisition.

T1-weighted neuroimaging data was acquired using a 3-Tesla Siemens Trio 3T scanner at the Hôpitaux Universitaire Genevois (HUG), or at the Brain Behavioral Laboratory at University of Geneva (BBL). A 3D volumetric pulse sequence was used, with the following parameters: TR = 2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 x 256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices.

MRI Pre-processing.

To obtain an accurate three-dimensional cortical model, images were processed using *FreeSurfer* software version 5.3 (http://surfer.nmr.mgh.harvard.edu). Processing steps were conducted following the *Freesurfer* pipeline for fully automated preparation of images, included resampling of the surface into cubic voxels, skull stripping, intensity normalization, white matter segmentation, surface atlas registration, surface extraction and gyrus labeling. After preprocessing, each participant was registered to the spherical atlas *fsaverage* in *FreeSurfer*. For each individual, resulting white matter and pial surfaces were visually checked and manually corrected when necessary. CT was measured as the shortest distance between the two surfaces and was computed at each vertex of both hemispheres. CT was smoothed using a full width at half maximum kernel of 10mm and the cortex was subdivided into 66 parcels based on the Desikan-Kiliani cortical atlas[24] provided in FreeSurfer. The parcellation of the brain translates in a ROI-based approach; we extracted 66 values of CT per participants (one per regions) covering the whole brain cortical areas.

To extract reliable thickness estimates, images were automatically processed with the longitudinal stream[27] in FreeSurfer. Specifically an unbiased within-subject template space and image[28] is created using robust, inverse consistent registration[29]. Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialized with common information from the within-subject template, significantly increasing reliability and statistical power. Although manual edits from the previous steps were incorporated in the longitudinal scans, each resulting scan was visually checked again, and manually corrected if needed. Note that individuals with a single time point were also processed through the longitudinal stream to ensure consistency of processing.

Statistical analysis: Descriptive statistics

First, we performed descriptive cross-sectional statistical analyses comparing the participants' subgroups obtained from clustering in order to investigate whether they differed on their demographic characteristics. Mann-Whitney U tests were conducted in SPSS Version 24.0 on demographic and cognitive variables including age, ASR/YSR internalized and externalized behaviors score, and Wechsler's WISC/WAIS-IV Block Design and Vocabulary standardized score. We additionally combined WISC/WAIS two subtests into a measure of intellectual functioning using the average of the subtests.

Statistical MRI analyses: Developmental Trajectories

We performed mixed model regression analyses[30,31,32] using in-house script to compare trajectories of CT between high and low level of each schizotypy dimension. Mixed modeling has proven to be a reliable method[30] for the statistical analysis of nested data, such as our dataset comprising multiple time points. Age and schizotypy groups were modeled as a fixed effect and within-subject factors as random effects using the nlmefit function in MATLAB R2016b (script available at https://github.com/danizoeller/myMixedModelsTrajectories). For each of the 8 analysis: sex, location of MRI scanner, ASR/YSR internalized and externalized behaviors scores, and an average score between Wechsler's WISC/WAIS-IV Block Design and vocabulary standardized scores were entered as mean-centered (demeaned) covariates of no interest.

Developmental trajectories were estimated by fitting random-slope models[32] to our data (constant, linear, quadratic or cubic, each corresponding to a different relationship between age and CT) while taking into account both within and between-subject effects. Then, the most suitable model order was selected based on the Bayesian Information Criterion[33]. For the individual dimensions, the grouping variable consisted of a vector with two levels (coded as 0: low SPQ scores and 1: high SPQ scores), for the three dimensions analysis, the grouping vector was coded with three levels (1: low, 2:intermediate, 3:high scorers). Finally, the significance of between group differences in the intercept and slope were evaluated using a log-likelihood ratio test. Thus, we obtained a comparison between the intercept (group effect) and the slope of developmental trajectories (group x age interaction effect) of the CT of each group. All retained results survived a threshold of $p<0.05$, corrected for multiple comparisons using False Discovery Rate (FDR). For more details, see *supplementary material*.

Results

1. Descriptive measures

1.1 Dimensional analysis

Descriptive statistics for the groups based on high and low scorers in each dimension of schizotypy at first time point are presented in Table1. For each analysis, all schizotypy dimensions and internalized behaviors differed significantly between high and low scorers. Whereas age and gender were balanced between groups.

1.2 Profile analyses

Descriptive statistics of the three groups created on SPQ scores on all schizotypy dimensions at first time points and representing schizotypy profiles are presented in Table2.

2. Structural MRI analyses: Developmental Trajectories

2.1 Dimensional analyses

When applying mixed model regression analyses for positive, negative and disorganized schizotypy separately, we found significant between groups differences in CT developmental trajectories for each dimension. Significant results are presented below; please refer to the *supplementary material* for results including all 66 regions.

Positive schizotypy dimension

For both groups, CT developmental trajectories of the left posterior cingulate cortex were linearly decreasing and displayed significant differences of slope in relation to positive schizotypal dimension (p=0.016, FDR-corrected for multiple comparisons), with HPS exhibiting quicker CT thinning compared to LPS over the entire age-range (*see Figure 2A*).

Disorganized schizotypy dimension

Among the 66 cortical regions studied, the caudal anterior cingulate showed a slower linear cortical thinning with age in adolescents with high disorganization scores compared to those with low disorganization scores (p=0.009, FDR-corrected, *see Figure 2B*).

Negative schizotypy dimension

In the left hemisphere, quadratic trajectories of CT in the pars triangularis, the rostral middle frontal and lateral orbitofrontal cortices showed significantly different slopes of the trajectories between HNS and LNS (respectively: p=0.045, p=0.004, p<0.000, all FDR-corrected). In HNS, CT in these three frontal regions showed a peak of thickness around 17 y.o, while CT of LNS followed a U-shaped-like decrease until its lowest measure around 20 y.o (*see Figure 2E, 2C, 2G*). In all regions, the maturation of CT is delayed in HNS, and followed by an accelerated cortical thinning.

In the right lateral occipital cortex, HNS displayed a peak of CT around 18 y.o, while the CT of LNS was at its highest at an early age and then gradually decreased until early adulthood, indicating a significant difference in quadratic trajectory slopes throughout adolescence (p<0.000, FDR-corrected, *see Figure 2D*).

Concerning the right isthmus cingulate region, LNS showed a gradual U-shaped-like thinning of CT, whereas HNS exhibited linear excessive cortical thinning compared to LNS over the entire age-range (p=0.011, *see Figure 2F)*.

2.2. Combined scores analyses

When examining the combined scores of the three schizotypy dimensions, HS, IS and LS displayed significant differences in the development of two cortical brain regions. In the R-isthmus cingulate cortex, CT trajectories were significantly different across all three subgroups *(*p=0.005, FDR-corrected) as well as in the R-lateral occipital cortex (p=0.005, FDR-corrected). In both cases, it seems when observing the figure, that CT followed quadratic U-shaped trajectory for the LS profile, an inverted U-shaped trajectory for HS and a linear trajectory for the intermediate group (*see Figure 3*). In the right isthmus cingulate cortex, LS displayed the highest CT in early adolescence, which gradually decreased over the covered age interval. HS exhibited the lowest CT in early adolescence in this region, with gradual thinning until early adulthood. Finally, IS adopted an "intermediate" linear developmental trajectory, positioned in between CT measures of HS and LS. In the right lateral occipital cortex, LS showed decreasing CT from age 12, while CT of HS remained at constant value until 17 y.o where a subsequent

slow decrease occurs until adulthood. Interestingly, IS again exhibited an "intermediate" linear CT developmental trajectory, relatively to HS and LS.

Discussion

This longitudinal study examined cortical thickness (CT) developmental trajectories in relation to the dimensions of schizotypy in a group of non-clinical adolescents. When examining the potential associations of each single dimension of schizotypy individually, we first observed that adolescents reporting a higher level of positive schizotypy showed an accelerated thinning within the left posterior cingulate cortex (PCC) CT. Furthermore, those adolescents reporting a higher level of disorganized schizotypy showed distinct pattern of CT development around the caudal anterior cingulate region when compared to lower disorganized schizotypy expression. In relation to the negative dimension of schizotypy, the development of CT in the prefrontal, occipital and cingulate cortices appeared to differ between adolescents expressing higher and those expressing lower levels of negative schizotypy. In our subsequent analyses, when examining subgroups clustered as high, intermediate, and low on all schizotypy dimensional scores, we observed distinct patterns of CT development involving two of the same regions as when investigating the negative dimension: PCC and lateral occipital cortices. This longitudinal study on schizotypy allows us to disentangle the extent to which structural brain abnormalities form part of a general vulnerability to the disorder or are only present in individuals who subsequently develop schizophrenia, thus characterized as markers associated with clinical risk. In the following discussion, we will assess, on one-hand, results involving the same brain regions as those involved in the neuroimaging studies examining clinical high risk CT trajectories of subjects who convert to psychosis. On the other hand, we will identify brain regions atypical CT developmental curves simply linked to inter-individual variability on the schizotypy trait. We will address this duality by comparing our results with existing longitudinal studies involving CHR converters and individuals at familial high-risk, as well as general population studies on schizotypy.

[High vs Low Positive dimension]

Adolescents expressing higher levels of *positive* schizotypy displayed a significantly more pronounced thinning of the PCC when compared to lower positive scorers. Similar abnormal thinning over time was found in the cingulate of individuals at familial high risk[34], suggesting that atypical CT development in this region may be a common genetic marker of general

vulnerability to psychosis. As some authors have suggested, a related cognitive endophenotype may relate to a failure to distinguish clearly between internal and external events, which in patients with schizophrenia links to reduced PCC volume[35,36].

[High vs Low disorganized dimension]

A slower linear cortical thinning trajectory was observed for the adolescents scoring high on disorganization schizotypy, in the right caudal anterior cingulate cortex CT, when compared with lower disorganized schizotypy scorers. Although the slope of the developmental trajectory was steeper in LDS, HDS displayed lower CT values until 18 years of age. In comparison, it has been found that the anterior cingulate cortex is thinner in familial high risk[34], as well as in patients with SPD[37], FEP[38] and schizophrenia[39]. It is thus tempting to interpret that the pattern found in HDS non clinical adolescents represents a form of compensation mechanism protecting them from the significant loss of GM seen in clinical populations, although future studies should examine more closely the mechanisms that would underlie this putative protective mechanism, which leads HDS and LDS to present equivalent CT after 18 years of age.

[High vs Low Negative dimension]

HNS showed a delay in right *lateral occipital* CT maturation when compared to LNS, with thinning only starting at around 18 y.o. Recent literature concerning the impact of psychotic symptoms on morphology of lateral occipital lobe reports CT reduction in unaffected relatives of schizophrenia patients[34,40], in first-episode schizophrenia patients[41], and schizophrenia patients[42,43]. The trajectory displayed within the *isthmus cingulate* cortex, with an excessive cortical thinning in adolescents expressing higher negative traits. The isthmus representing the posterior part of the cingulate, and as mentioned above, the observed atypical trajectory of CT is retrieved in unaffected familial high risk[34] and seems to be related to the symptomatology of schizophrenia such as failure in differentiation between internal and external thoughts explained earlier[35]. This may influence the cognitive endophenotype associated with schizotypy, but not necessarily contribute to the emergence of psychotic disorders.

Expressing high *negative* schizotypy was also associated with delayed maturation and later decrease of CT in three *prefrontal* regions (pars triangularis, orbitofrontal and middle frontal cortices). LNS displayed a slightly U-shaped decrease of CT in each prefrontal region, concordant with studies investigating CT development in typical adolescence[44], while HNS

exhibited an inverted U-shaped increase trajectory. Cannon and colleagues[10] showed that CHR converters exhibited steeper rate of GM loss in superior and middle frontal and medial orbitofrontal regions when compared to non-converters and HC. Our results further relate to findings of Yoohnho and colleagues, who showed that CHR converters at follow up exhibited smaller surface area in lateral and medial prefrontal regions[11]. In conjunction with clinical evidence suggesting that negative schizotypy (mostly anhedonia) rather than positive schizotypy might be more predictive of conversion to CHR states[3], these prefrontal alterations may speak directly to emerging risk states and conversion to clinical forms of psychosis.

[Schizotypy profiles]

Consistently with some studies using the SPQ total score, our analysis with this sum score yielded differential CT development of the right *isthmus cingulate* cortex and right *lateral occipital* cortex in HS, IS and LS. In HS, maturation of CT in these regions appeared delayed, and followed by significantly more pronounced thinning. Interestingly, IS display intermediate CT developmental trajectories in these two regions, in between that of HS and LS. We could hypothesize that this last result illustrates the continuum of psychosis theory[45], with significant focal relationships between cerebral maturation and degree of expression of schizotypy. Several studies have reported reduced CT in schizophrenia, with intermediate measures of CT in frontal and cingulate cortex in relatives[46] or in SPD patients[47], compared to healthy controls. In addition, in a study comparing psychotic patients, non-clinical auditory hallucinations and healthy controls, it was shown that CT in temporal lobe is intermediate in the non-clinical hallucinating group, lowest in patients and highest in controls[48.] Thus, in the present sample of adolescents, we could argue that a similar process is already active at the non-clinical stage in two key regions known to be involved in internally directed thoughts and visual processing. Similarly, individuals expressing higher schizotypal personality traits present the most atypical CT trajectory when compared to low schizotypy profiles. Moreover, although the association of schizophrenia's visual hallucinations and the occipital lobe is known, whether the whole occipital lobe is involved or just some parts or whether it is damaged before other regions remains open to investigation (see review)[37]. Here, we can only infer on the differential trajectory in the three schizotypy profiles and hypothesize that CT in these regions follows a similarly gradual atypical CT development which could relate to specificities in information processing, but this remains to be thoroughly researched. Strikingly, the two regions identified in the present profile analysis correspond to two of the regions showing atypical developmental

trajectories in adolescents expressing higher negative schizotypy. This last observation seems to corroborate the hypothesized psychosis-predictive role conveyed by the negative dimension in those regions.

[Limitations]

There are a number of limitations to this study that should be taken into account. We investigated developmental trajectories only during the second decade of life and throughout adolescence; therefore, similar attention could be given to major changes appearing during childhood. Secondly, the main analyses were conducted with FreeSurfer, parcellating the brain using an atlas from the software, which is consistent with most of previous literature and allows the use of indices of fit for model selection. However, for larger parcellated structures, it is important to bear in mind that developmental patterns might be different within regions. Another limitation is the use of a self-rated instrument; future studies should include an observer rater (interviews). While longitudinal schizotypal traits studied in the general population is still a burgeoning field, further research using larger cohorts is required. Importantly, cohorts of adolescent siblings of patients with schizophrenia would help evaluate the strength and value of the results found in our general population sample We contend that enhanced longitudinal characterization (with more time points or following the converters to psychosis) will provide fruitful grounds for uncovering the developmental processes preceding high-risk states that signal pathogenic markers, and may eventually inform prevention strategies.

[Conclusion]

This longitudinal study allowed us to draw new hypothesis concerning the common cerebral endophenotypes between adolescent schizotypy and CHR, siblings, and well as clinical samples. However, given the lack of direct comparison between these populations, future research is required to validate the potential risk-predictive value of negative schizotypy in clinical population and to understand the mechanisms driving the differences as well as their functional and behavioral implications.

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